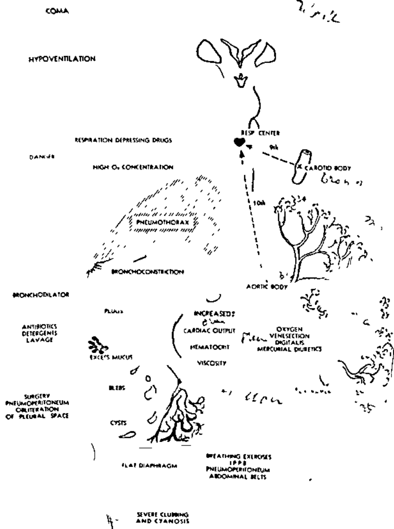
CHRONIC PULMONARY EMPHYSEMA



FRONTISPIECE

odern Medical Monographs 8

CHRONIC PULMONARY EMPHYSEMA

Physiopathology and Treatment

By MAURICE S. SEGAL, M D

Clinical Professor of Medicine, Tufts College Medical School, Director, Department of Inhalational Therapy, Boston City Hospital

and M. J DULFANO, M D

Resident, Department of Inhalational Therapy Boston City Hospital, Research Fellow in Medicine, Tufts College Medical School



GRUNE & STRATTON · New York

1953

GRUNE & STRATTON, INC
381 Fourth Avenue
New York City 16

Printed in U S A for Grune & Stratton

Preface

During the past several years it has been my privilege to conduct a series of lectures on the treatment of chronic pulmonary emphysema This book is a presentation of the principles and methods discussed therein as the result of laboratory research and practical clinical experience

An attempt has been made to integrate the physiologic aspects with the treatment of chronic pulmonary emphysema In the general outline, we have kept in mind the clinical manifestations and complications, particularly respiratory acidosis and pulmonocardiac complications, symptomatic treatment, specific therapeutic measures, and have attempted to correlate the patient's clinical manifestations with the impairment of his cardiopulmonary function Pulmonary function studies appear in Chapter III, details of cardiopulmonary function testing appear in the Appendix Methodology Division of *the subject into 13 specific chapters and Appendix is arbitrary*

A proper understanding of the clinical course in chronic pulmonary emphysema and rehabilitation of the patient by application of the measures discussed in this book require physiologic integration The cyanotic, gasping, hypoxic patient may suffer harm, or even die, from "paradoxic therapeutics" if the therapeutic agent he needs most —oxygen—is improperly administered Cardiopulmonary function studies reveal the defects at various stages of the disease and can actually be prognostic of the extent to which many of these defects are reversible Adequate therapy directed on sound physiologic principles may promote improvement in ventilation and perfusion, correction of electrolyte imbalance, reduction in pulmonary arterial hypertension, and prevent the development of irreversible cardiac damage and failure

The advent of the new antibiotics and hormones has made it almost mandatory that the diligent physician review bacteriology and

reactions of the patient-host have mellowed our judgment and prepared us for the third stage of benign resignation Unfortunately,

the early hopes of eradicating heterogenous bacterial populations with antibiotics and increasing the ability of the patient to withstand the effects of a variety of stressors by the use of hormones, thereby increasing the longevity of the patient, have not been fully realized.

The patient is aided considerably toward rehabilitation by the physician who can also administer to his mental needs Such a patient is easily discouraged and finds it difficult to accept the disability that is caused by the symptom cough, wheeze, or shortness of breath. The prospect of many years of progressive disability because he has an improperly functioning breathing apparatus is even more difficult for the patient to accept, and requires more skillful handling. In explaining the nature of the illness, the physician who is not wary at all times may inadvertently introduce iatrogenic lung disease

Change of occupation, or of residence for "climatic relief," and the use of occupational therapy are problems requiring careful consideration The physician should diligently and impartially evaluate all the etiologic factors before concluding that the patient's disease is occupational in origin Complete cardiopulmonary function tests can weed out malingerers and accurately determine the degree of disability The change in midposition of the lung, the ratio of residual volume to total lung volume, and the pressure in the pulmonary artery will definitely determine the true extent of the disease.

Unfortunately, many patients with progressive chronic pulmonary emphysema are not able to obtain the treatment prescribed, because application of many of the newer therapeutic principles may throw too great a financial burden on the patient and his family To many patients, unfortunately, therapeutic rehabilitation amounts to an "economic prescription" they cannot fill Our social economic structure makes it possible for those at both extremes of financial status to obtain the needed help In this day of social enlightenment, however, it appears likely that these benefits will become available to all

Judicious application of the therapeutic principles described should make it possible to give the patient with chronic pulmonary emphysema a much more optimistic outlook than was previously possible.

Acknowledgments

In the preparation of this text, I am indebted in a general way to former residents and technicians who toiled faithfully to accumulate the physiologic data leading to some of the ideas herein expressed. To one of our former residents, Dr. J. A. Herschfus, I am most grateful for help in obtaining and assembling our data and material for the sections on pulmonary function and for aid in the preparation of several of the figures shown. Dr. L. Levinson read an early draft and made many valuable suggestions as to content and presentation.

I am happy to acknowledge my indebtedness to our technicians, the Misses Dorothy J. Mellen and Doris J. Grossman, though busy with Van Slyke, Scholander, and bacteriologic studies, they found time for charts, tables, figures, and innumerable other chores. The Misses Betty Karasik and Margaret Little read and edited parts of the manuscript and made many helpful suggestions.

I am grateful to those who loaned material for illustrations. Dr. S. L. Robbins of the Mallory Institute of Pathology, Boston City Hospital, for permission to use Figs. 3, 4, and 5, Dr. D. Littman of the Veterans Hospital in Boston for the use of Fig. 16, Dr. S. Dressler of the Jewish National Hospital in Denver for the use of Fig. 25, Dr. I. Ferrer for permission to reproduce Fig. 19, and Dr. F. Fleischner of the Beth Israel Hospital, Boston, who patiently reviewed our roentgenograms and permitted the use of Figs. 10, 11, 12, 17, and 18.

To my loyal secretary, Miss Lettie H. Robidou, I am particularly indebted. With rare understanding and consummate skill she has permitted my Stress to continue unabated. She translated my scribbling, typed many drafts of the text, proofread other secretaries' typing efficiently and calmly despite many other exacting duties.

I was most fortunate to have the assistance of my Resident, Dr. Mauricio J. Dulfano of Israel in the preparation of this book. Always devoted and loyal, his zeal and criticism stimulated the intent of exacting standards and presentation. "The observation at bedside must have laboratory confirmation!" always met with his approval. I feel that I have deprived him of much during this past year and have gained much more. The results are evident.

MAURICE S. SEGAL, M.D.

Boston, March, 1953

Contents

List of Illustrations

List of Tables

To those we respect and love

They will readily recognize their influence

CHAPTER I

Introduction and Classification

The term *emphysema* is derived from the Greek ἐμφύσημα or *emphysan*, which means "to blow into, to inflate" It is used to designate a variety of states in which overinflation occurs, either in the lungs or elsewhere in the body. Overinflation of the alveolar sacs, *pulmonary emphysema*, may be purely physiologic (functional) or it may be associated with definite pathologic (anatomic) changes

Confusion exists in the multiplicity of terms and classifications that have been employed to describe the different types of emphysema Pulmonary emphysema may be acute or chronic, and the involvement may be local, unilateral, or diffuse Although usually associated with other disorders of the heart, lung, chest, or spine, emphysema may occur independently (see Fig 1).

Nonpulmonary Emphysema

Nosological misnomers have served to confuse all these conditions Although *interstitial emphysema*, also called *interlobular* or *mediastinal emphysema*, does frequently involve interstitial spaces between alveoli or bronchi, it is not a true alveolar emphysema The term should be reserved for describing those cases in which air escapes from the alveoli or bronchi into the interstitial connective stroma of the lungs and thence finds its way along the perivascular and peribronchial sheaths into the mediastinum [104] The air may further dissect its way into pleural and peritoneal cavities, retroperitoneal spaces, and subcutaneous tissues in the upper part of the chest and base of the neck

Roentgenograms in such cases may reveal air bubbles like tiny pearls along the bronchi and vessels [171] In short, air enters and collects in tissues that do not normally contain gas The manifestations vary with the underlying disorder responsible for the interstitial pulmonary emphysema and the degree of circulatory or respiratory

embarrassment resulting from the presence of air under tension (airblock) Although the amount of air may be small and resorbed rapidly, and the patient relatively symptom-free, pain, cough, and dyspnea are frequently noted. The sudden onset of chest pain, associated with an unusual crackling or crunching sound that is at times audible away from the chest wall (Hamman's sign),[79] indicates the presence of a spontaneous mediastinal emphysema. The pain and dyspnea should be relieved by aspiration of the airblock. Dyspnea that persists requires search for the possible presence of a tension pneumothorax, relief of which by water-sealed drainage may alleviate discomfort and occasionally prove lifesaving The inhalation of 100 per cent oxygen will accelerate solution of the bubbles of gas by

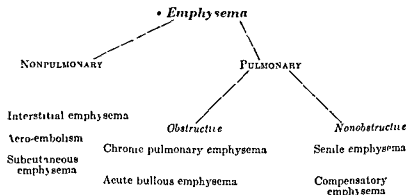


Fig 1 —Classification of emphysema

"washing out" nitrogen from the alveolar air and the circulating plasma

Aero-embolism, or *tissue emphysema*, is also not a true alveolar emphysema This problem has been intensively studied in divers and caisson workers and in aviation medicine [25] It is usually referred to as "the bends," inasmuch as joint pain is the most common symptom In rapid ascents to high altitudes, in the experimental low-pressure chamber, or in actual flight without the protection of pressurized chambers at levels above 25,000 feet, the aviator encounters not only the effects of oxygen want but the effects of the greatly lowered barometric pressure Oxygen breathing will not protect against the latter. Under such conditions, nitrogen is liberated in gaseous form into the

blood or tissues, producing bubbles of gas (aero-emboli), like bubbles that appear when a bottle of charged water is opened Similar changes occur in rapid ascents from depths where the diver or caisson worker has been exposed to pressures of about seven atmospheres, for example If the ascent is very slow and the circulation of the diver or aviator is adequate, the symptoms may not be too severe, for the nitrogen will be carried in solution to the lungs and eliminated

The manifestations depend upon the location of the bubbles, which consist largely of nitrogen and water vapor Early symptoms may be noted of skin itching, crepitus, paresthesias, and severe joint pains, particularly of the knees and shoulders ("the bends") The joint pains are particularly disabling The central nervous system may be affected The lungs may be involved by pulmonary emboli, producing cough, pain, and asthmatic breathing—the so called "chokes" This requires immediate therapy, which consists of attempts to force the gas bubbles back into solution by increasing the atmospheric pressure—through rapid descent of the plane in actual flight, pressure manipulation in the low-pressure chamber in experimental work, recompression in a pressure chamber, or descent of the diver to deeper levels

Among other varieties of nonalveolar emphysema to be noted are the crepitation of subcutaneous gas in clostridial infections and the subcutaneous infiltration of air after chest injuries

Pulmonary Emphysema

States of pulmonary overdistention fall into two groups, according to their pathogenesis In both groups the common pathologic change is an increase in the size of the alveolar sacs This process results from an alteration of the normal pressure relationships during respiration, between the alveoli and the intrapleural space on the one hand, and between the alveoli and the lumina of the large bronchi on the other

Under normal conditions there is little or no appreciable pressure difference between the alveoli and the trachea, there is a slight variable difference between the intra-alveolar pressure and the intrapleural pressure, the latter always tending to pull the surface of the lungs outward (See Chapter II) As this sucking force—the intrapleural negative pressure—increases over a long period of time, the size of the lung increases with it, with distention of alveoli and the

development of pulmonary emphysema of a nonobstructive type. On the other hand, chronic partial bronchial obstruction will develop an abnormal pressure difference between the alveoli and the larger air passages and will result in a decreased expulsion of air in expiration Progressive air-trapping leads to alveolar overdistention and to pulmonary emphysema of an obstructive variety.

Regardless of the mechanism, simple overdistention of the alveolar sacs should not be called true chronic pulmonary emphysema, for the latter involves the presence of definite pathologic changes in the very structure of the parenchyma and blood supply.

Senile emphysema, also called *atrophic* or *postural emphysema*, is a nonobstructive form of pulmonary overdistention, associated with other atrophic and involutionary changes observed with aging There is good diaphragmatic and upper abdominal muscle function, which is not so with obstructive emphysema. The lungs are usually small and collapse readily when the chest is opened. There is good evidence that the alveolar distention is not caused primarily by loss of elasticity but is due to degenerative changes in the thoracic spine[94] Degeneration and marked swelling in the nucleus pulposus have been described in these patients There appears to be little impairment in pulmonary function and the disease is usually of no serious significance This has been further confirmed by pulmonary function studies in healthy elderly subjects[75]

Compensatory emphysema, also called *ectatic emphysema*, is a simple nonobstructive overdistention of lung segments or of an entire lung, at times accompanied by a simultaneous shift of the mediastinum. It occurs secondary to atelectasis, compression, fibrosis, or surgical resection of contiguous lung segments or of the opposite lung. An area of obstructive emphysema may be accompanied by compensatory emphysema in an adjacent area. Compensatory emphysema represents the intrathoracic readjustment by lung parenchyma to contiguous spatial shrinkage—in other words, a response at least partially compensatory in nature The extent of the emphysematous process depends on the ability of the lung tissue to enlarge and fill in the spatial shrinkage, in response to the intrapleural negative pressure ("sucking"), and on the facility with which the mediastinal structures, diaphragm, and thoracic cage can enter into the compensatory adjustments

In the early stages the ventilatory surface of the overdistended

lung is increased, and this may actually compensate for the spatial shrinkage. Compensatory emphysema may disappear on correction of the cause, obstructive atelectasis, for example. On the other hand, permanent compensatory emphysema, particularly of an entire lung, actually impairs ventilatory function. If the overdistention persists for a long time, resilience of the lung may be lost, giving rise to parenchymal atrophy and other irreversible structural damage similar to the changes in chronic pulmonary emphysema. Awareness of this complication has lead the thoracic surgeon to perform thoracoplasties to prevent extensive degrees of compensatory emphysema in the contralateral lung after pneumonectomy.

Acute bullous, or *vesicular, emphysema* is generally a serious and frequently fatal complication observed in children with asphyxia secondary to severe bronchial involvement due to whooping cough, measles, influenza, acute tracheobronchitis, or bronchopneumonia, in patients who suffocate from noxious irritants, gases, or drowning, and in patients with bronchial and cardiac asthma. It is actually a fulminating form of obstructive pulmonary emphysema. The lungs become severely overdistended as the result of extreme inspiratory efforts and bronchial obstruction ("effort lung"). Asphyxia and death may follow. If the underlying disorder can be vigorously and adequately managed, the disease may be partly or wholly reversible. If the obstruction and infection persist, a chronic type of pulmonary emphysema with bullous formation will persist.

Chronic pulmonary emphysema is also known as *hypertrophic, essential, substantial, alveolar, vesicular, inspiratory, expiratory, functional* or *structural, irreversible, large-lunged, hypoxic*, and *obstructive emphysema*. It occurs more commonly in men and the middle-aged. The differences that have been noted in the symptomatology, in pulmonary function studies, and in the varied results of special therapeutic procedures, such as intermittent positive pressure breathing and pneumoperitoneum, can be explained on the basis of the numerous lung disorders with which chronic pulmonary emphysema is associated. Determination of the underlying cause is important. It may appear as a primary disorder, idiopathic chronic pulmonary emphysema.

This form of pulmonary overdistention has been explained by Mayer and Rappaport on the basis of congenital insufficient lung parenchyma leading to defective post-natal development. They believe that it starts as a functional disturbance of the lungs which

may eventually become complicated by bronchial obstruction or pathological processes in the lung parenchyma.

Chronic pulmonary emphysema is generally believed to be the direct result of chronic bronchitis. It occurs with, or as a complication of, practically all pulmonary diseases—particularly severe bronchial asthma, bronchiectasis, serious pulmonary infection, the pneumoconioses, sarcoidosis, and tuberculosis. Chronic pulmonary emphysema, the major subject of this book, is one of the most distressing of the diseases of the lung.

CHAPTER II
The Development of Chronic Pulmonary Emphysema

We prefer the term "chronic pulmonary emphysema," defining it as the diffuse, progressive, obstructive, and hypoxic type of chronic emphysema in which pathologic distention of alveoli has persisted for some time Since chronic pulmonary emphysema is produced as a result of alterations in the pressure relationships between the various structures within the thorax, a clear understanding of these pressure relationships as they exist in normal health is essential for comprehending the forces that lead up to, aggravate, and perpetuate the condition

I. Intrathoracic Pressure Relationships—In Health

In utero, the thorax of the fetus is collapsed There is no air in the lungs Although frequent "respiratory" movements of the rib cage and diaphragm have been described, these are very small in extent When the child is born, and placental gas exchange ceases, there is an increase in the partial pressure of carbon dioxide in its blood, stimulating the medullary respiratory center, or, more precisely, the apneustic portion of the respiratory center A volley of nerve impulses is sent out, causing forceful co-ordinated contraction of the external intercostal muscles and the diaphragm The ribs lift upward as the external intercostal muscles contract, also moving outward and forward because of their form and their articulations with the vertebrae There is a resultant increase in the anteroposterior and

side-to-side measurements of the chest. The simultaneous contraction of the diaphragm increases the vertical dimension of the chest as well, so that the volume of the chest is greatly increased

Within the chest at the beginning of this first inspiration, the lungs are completely collapsed Diffusely distributed throughout the collapsed lung tissue are elastic fibers When the lung is in the collapsed state that exists in the fetus, these elastic fibers are at rest They resist stretching in the same way that a rubber band resists; that is, they can be stretched but they pull back against the elongating, stretching force As the first inspiration proceeds, the increasing volume of the thoracic cavity forces the lungs to expand at the same rate, since the parietal and visceral pleural layers are inseparable. The bronchi and trachea form a direct line of communication from the interior of the lungs to the outside air; as the lungs expand, air rushes into them to fill the air passages and alveoli

Let us now consider the pressure relationships between various segments of this apparatus during the first—or any subsequent—inspiration The alveoli expand and air moves into them from the outside, *via* the tracheobronchial tree, but because the walls of the trachea and bronchi exert a frictional resistance to this air movement, air cannot move toward the alveoli fast enough to keep them filled with air at atmospheric pressure This results in a rarefaction of the air which is in the alveoli at any instant

Differently expressed, the pressure during inspiration will be slightly less in the alveoli than in the trachea (or outside the body), the pressure in the trachea being governed by the degree of frictional resistance to the flow of air produced by the trachea and bronchi This gradient of pressure from outside air to alveolus during inspiration is never very large in health—about 1 or 2 cm. of water pressure.

Governing factors in the pleural cavity are quite different. This space between the lung and chest wall is only a potential one, as the parietal and visceral pleura are in apposition except for a thin layer of lubricating fluid But although no space actually exists, and although the visceral and parietal layers of the pleura cannot actually separate unless air or fluid enters the pleural cavity, a tendency does exist for these two layers to separate. This tendency arises from the elastic recoil of the lung When a rubber band is stretched, it cannot shorten while it is still held taut but an inclination toward shortening persists nevertheless, inherent in the elasticity of the material.

The existence of this tendency of the two pleural layers to separate can be demonstrated and measured, by puncturing the chest wall and connecting a manometer to the pleural space, with the other side of the manometer remaining open to the atmospheric pressure of outside air. The fluid in the manometer will rise on the side connected to the pleural space, demonstrating that pressure within the pleural space is less than that of the outside atmosphere ("negative" pressure). The magnitude of this tendency toward separation of the two pleural surfaces, measured in this way, is about 6 cm. water pressure during inspiration.

At the end of inspiration the lungs have been stretched maximally and the negative pressure in the intrapleural space is most pronounced. The flow of air into the alveoli has ceased, and at this point there is no pressure difference between alveoli and trachea.

With expiration, the sequence of events is reversed. Cessation of contraction of the external intercostal muscles and the diaphragm leads to contraction of the thoracic cavity as the ribs fall downward and inward because of their weight. In health this represents an essentially passive mechanism. In addition, the tendency of the lung to return to its collapsed state because of its elasticity is now greater than the outward pull of the chest wall. As a result of these several forces, the chest cavity becomes smaller and air is expelled. In this process, a reverse pressure gradient is set up between alveoli and trachea, as air flows outward. As the lung returns to a smaller volume, the tension on the elastic fibers lessens, and the degree of intrapleural negativity is decreased. But after the first breath of the infant, the lung never again becomes empty, and therefore the elastic fibers never return to a state of complete rest, the intrapleural pressure remains less than the atmospheric, even during expiration (about −2 cm. water pressure).

The degree of negative pressure built up in the pleural space during inspiration is the sum of pressure differences between the pleural space and alveoli and between the alveoli and outside air. If there were no inflow of air into the interior of the lungs, expansion of the thoracic cavity during inspiration would create an enormous degree of negative pressure between the chest wall and the now inexpandable lungs. This inspiratory force can be measured by forcible "sucking" on a rubber tube connected to a mercury manometer, pressures of from −40 to −50 mm. Hg can easily be attained. The attainment

of this degree of negativity in the trachea would presuppose an even greater negative pressure in the intrapleural space

In health, such extremes of intra-alveolar and intrapleural negativity do not develop, because the frictional resistance to airflow exerted by the trachea, bronchi, and bronchioles is small. Greater degrees of intrapleural negative pressure in inspiration will obviously develop from partial bronchial obstruction to the inflow of air. However, in expiration partial bronchial obstruction may also increase the resistance to the outflow of air so much that the intrapleural pressure may become greater than the atmospheric (more positive)

The elasticity of the chest wall and that of the lung parenchyma together seem to play the most important part in normal respiration, reciprocating dynamically in harmonious interrelationship according to the state of expansion of the lungs Their respective forces, although equal, are opposed at the normal resting point or midposition (end of quiet expiration) At the height of maximum inspiration, lung elasticity is a strong force and chest elasticity a weak one, at that moment, both forces exert themselves toward expiration At the point of maximum expiration, this process is reversed. In a healthy individual, the total vector of these forces is of equal magnitude but in opposite directions at both extremes of maximal respiratory effort

II. Intrathoracic Pressure Relationships—In Bronchial Obstruction

Bronchi and bronchioles are normally longer and wider during inspiration than they are during expiration, since they participate in general expansion of the lung as the chest cavity enlarges, and return toward a resting state when it becomes smaller on expiration. Partial bronchial obstruction to a degree that is of little or no significance in inspiration may increase to an extreme degree during *expiration*

Let us assume that enough edema develops in the wall of a bronchus to decrease its diameter by 1 mm. If that particular bronchus ordinarily has an inside diameter of 4 mm. during inspiration, it will now be decreased to 3 mm If the expiratory diameter is normally 2 mm , it will now be 1 mm The rate of airflow, however, is proportional to the cross-sectional area of the bronchus. The inspiratory cross-sectional area, normally 12 57 mm.^{2}, is reduced by the develop-

ment of edema to 7 07 mm², a decrement of 44 per cent The normal expiratory area of 3 14 mm² is reduced to 0.79 mm², a decrease of 75 per cent

The accentuated degree of partial bronchial obstruction during expiration explains the preponderance of expiratory wheezing noises, air during expiration has to pass through bronchi not only normally narrowed but highly constricted as well The sounds can be detected through auscultation of the lung, but are best heard with the stethoscope at the open mouth

Derangement of the pressure relationships within the chest after partial bronchial obstruction is the common denominator in the diseases of the respiratory tract (bronchial asthma, tuberculosis, silicosis, and other pneumoconioses) that lead to the development of chronic pulmonary emphysema Partial bronchial obstruction frequently occurs with bronchial asthma and produces an obstructive emphysema, a "functional blackout of the lung"

Asthma and all the other underlying pulmonary diseases are invariably accompanied by a diffuse type of bronchiolar obstruction, retardation of expiratory airflow, and cough These lead to a chronic state of alveolar distention and subsequently to dilatation of the alveolar ducts, enlargement of the air sacs, rupture of the interalveolar septa, atrophy and fragmentation of the alveolar walls, and formation of large alveoli or bullae from the remains of two or more of the original alveoli

What causes these changes is the selective trapping of air in the portions of the lung distal to the area of partial bronchial and bronchiolar obstruction With inspiration, the bronchiolar cross-sectional area is greater, and in response to the higher degree of intrapleural negative pressure, air flows into the alveoli, although with less ease than under normal conditions With relaxation of the muscles of inspiration, the bronchi contract, and now the elastic recoil of the lung and the weight of the chest wall are forces insufficiently powerful to overcome the resistance to egress of air from the alveoli through the augmented expiratory bronchial or bronchiolar obstruction The alveoli therefore do not empty as completely as under normal circumstances, the elastic recoil of the lung is thereby further impaired, and alveolar distention increases progressively as more and more air is trapped in the alveoli with each succeeding breath

The role of partial bronchial obstruction in the development of

chronic pulmonary emphysema, first suggested by Laénnec,[96] has been the subject of many interesting recent studies. Matheson *et al*[109] introduced airflow resistance experimentally in healthy young adults but were unable to produce appreciable diminution of vital capacity. The tolerance of the pulmonary elastic recoil in healthy young adults to airflow resistance during an acute experiment cannot be compared with that of the patient in whom resistance to the flow of air has existed for many years.

In addition, these experiments involve the creation of an artificially increased pressure gradient between the trachea and the outside atmosphere, this is not necessarily directly comparable to constriction of the smaller bronchi and bronchioles, where the abnormal pressure gradient is between the alveoli and the trachea and larger bronchi Not only is a decrease in vital capacity the rule in clinical asthma, but expiration becomes progressively more prolonged and the vital capacity tends to fall with successive attempts at its measurement, as more and more air is trapped in distended alveolar sacs behind the constricted bronchioles.

It has been observed bronchoscopically in patients with emphysema and bronchial asthma that the bronchial walls collapse during expiration, especially with forced expiration.[124] In the patient with emphysema, this finding has been explained on the basis of a progressive increase in alveolar volume, as the result of the loss in elasticity, without a corresponding increase in the cross-sectional area of the air passages leading to the alveoli

At the start of expiration, therefore, when intra-alveolar pressure rises above the intrabronchial pressure, the bronchi and bronchioles lying between the alveoli become compressed and more narrowed than in a normal lung during expiration, increased resistance to expiration results.[124] This mechanism leads to slowing of the rate of air flow during expiration and permits emptying of the lungs to a normal degree only by prolonging the expiration. By roentgenograms, Westermark[171] has demonstrated the existence of solitary or multiple alveolar blebs, located centrally in the lung parenchyma, surrounded by an atelectatic border zone. He attributes this atelectatic area to a compression of normal lung tissue by the increased intra-alveolar pressure in an expanded adjacent emphysematous area

Dayman[50] recently carried out rather extensive airflow resistance

studies, using a modified pneumotachograph, in patients with chronic pulmonary emphysema He concluded that the bronchoconstriction was due to an expiratory check valve mechanism on the terminal bronchioles originating from the distended alveoli induced by the increased expulsive force necessitated by the retarded expiratory airflow This is in essential agreement with the conclusions of Proctor and his group [125]

The net elastic recoil of the lung, or lung tension, measured under static conditions, represents the pressure required to maintain distention of the lung In healthy individuals it bears a direct relationship to lung volume A reduction in the lung tension (elastance), resulting from the breakdown of lung parenchyma, leaves the bronchioles architecturally weak and subject to easy collapse by pressure from the distended alveoli as well as by the development of a positive intrapleural pressure during expiration Dayman agreed that lung tension was decreased in four of his patients who had advanced emphysema but felt that it was not justifiable to conclude that the remaining tissue in such lungs had necessarily lost elasticity [50]

Simple physiologic (functional) overdistention of the lung alveoli will not produce the definitive anatomic and physiologic changes associated with chronic pulmonary emphysema This probably explains the infrequency of this disease among persons whose occupations involve increased respiratory efforts, such as players of wind instruments, glass blowers, etc

When the factor of bronchoconstriction is introduced, however, intrabronchial and intra-alveolar pressures may be considerably increased during expiration This occurs particularly during coughing, sneezing, straining at stool, shouting, screaming, and singing,—acts performed with the glottis or pharynx closed, followed by sudden forced expiration while the diaphragm moves rapidly upward In coughing and violent sneezing, the intrapulmonary pressures are rapidly, though momentarily, increased above atmospheric

During coughing paroxysms in patients with chronic pulmonary emphysema, these pressures are notably increased and contribute to the progressive overdistention So long as the cough persists, the elevated intrapulmonary pressure will persist within the obstructive emphysematous lung The air trapped in the distended alveoli cannot escape through the constricted bronchiolar lumina It may gradually

be resorbed if the pulmonary circulation is adequate, but alveolar overdistention will recur when paroxysmal cough next returns with its cycle of bronchoconstriction and rise in intrapulmonary pressure The overdistended, inelastic lungs balloon out, and even extend beyond the confines of the thoracic cage by pressing the diaphragm downward and infringing upon the abdominal viscera

The expiratory phase of respiration is normally passive, and the pulmonary elastic recoil results in an effortless decrease in lung volume as the diaphragm ascends with expiration In the patient with chronic pulmonary emphysema, all the accessory muscles of respiration must be employed to elevate the intrapleural pressure—even to levels considerably above atmospheric—enough to force an adequate amount of air out of the chest

Impaired inspiratory distensibility and impaired expiratory recoil of the lungs thus develop as a result of abnormal air inflow and outflow patterns Progressive alveolar distention follows. Prolonged alveolar distention eventually leads to rupture of interalveolar septa As adjacent alveoli become larger and larger, the wall between them is stretched more and more until eventually it tears, the resilient portions of the torn membrane spring back, and the two alveoli become one larger bleb In this fashion the number of air sacs gradually decreases and their average volume increases

The Macklins[104] have demonstrated that a definite pressure gradient must be created before alveolar rupture follows overinflation of the lungs The alveoli can withstand high internal pressures that are distributed equally to the surrounding alveoli Destruction of interalveolar septa has several effects As the volume of each coalescing air sac increases, the ratio of surface area to volume decreases, since these sacs are roughly spherical The surface of these spheres constitutes the surface area available for the exchange of respiratory gases between the air in the alveoli and the blood in the pulmonary capillaries, and therefore the rupture of interalveolar septa leads to reduction of the available respiratory exchange membrane.

While the number of air sacs is decreasing and the volume of each coalescing air sac is increasing the volume of air not actively involved in gas exchange is increased as dead space. With the eventual formation of macroscopically visible blebs, this factor of increased dead space may become very large Irregular and inadequate ventilation of such blebs, particularly in areas near the hilum, may produce a

virtual veno-arterial shunt by allowing unoxygenated pulmonary venous blood to pass into the intact arterial stream, thus increasing the small physiologic amount of venous admixture.

As a result of these several factors, the rate of total oxygen uptake by the blood in the pulmonary capillaries may become inadequate, with a resulting fall in the partial pressure of oxygen in the arterial blood, a reduced arterial oxygen saturation, and a decrease in the amount of oxygen available to the tissues (hypoxia) The hypoxia is thus a direct result of the increase in the dead space ventilation

Distended airfilled alveoli trapped behind constricted bronchioles reduce pulmonary elasticity by preventing elastic recoil of the lung Nevertheless, there is no anatomic loss of elastic fibers The fibers are still present, even though the increased resistance to expiratory outflow of air in the alveoli limits their contraction (functional loss) On the other hand, with destruction of interalveolar septa, elastic fibers rupture from their attachments and return to a state of rest —even though the lung is still overexpanded, just as a rubber band snaps from fatigue or plastic deformation when it is strained beyond its elastic limit In this way, destruction of interalveolar septa adds a loss of parenchymal elasticity to the functional loss effected by bronchoconstriction

It appears that the following sequence of events occurs after bronchoconstriction.

A Increased expiratory intra-alveolar pressure During this early phase the lung tension may remain intact or even increase

B Maintenance of this increased pressure leads to breakdown of normal parenchymal architecture and to a decrease in lung elasticity and tension

C Decreased expiratory intra-alveolar pressure, assisted by positive intrapleural pressure (checkvalve mechanism) At this point lung tension is significantly reduced

These successive derangements of function—bronchoconstriction, loss of alveolar structure and elasticity, and loss of parenchymal elasticity—which lead to the development of chronic pulmonary emphysema may be due to any of a large number of underlying causative factors The fundamental causes may be allergic, infectious, occupational, degenerative, mechanical, or constitutional in character

Progressive evidence of pulmonary insufficiency, ranging from the

abnormalities in alveolar ventilatory function to the effects of hypoxia and hypercapnia, may be observed as the disease process continues and advances The effects of hypoxia and infection may contribute further structural change, such as increased interstitial atrophy, loss of elastic tissue, progressive fibrosis, and obliteration of blood vessels Ultimately, through the continued tidal pull of the satellites (respiratory infection and bronchoconstriction), serious pulmonocardiac complications appear in the form of pulmonary arterial

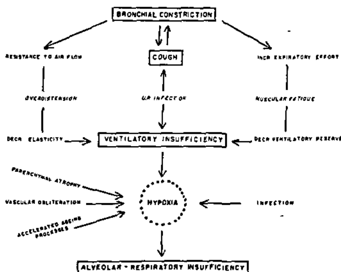


FIG 2 —Factors involved in the development of pulmonary insufficiency

hypertension, chronic cor pulmonale, and electrolyte disturbances. The above factors are schematically represented in Fig 2

III. Pathology

The gross pathologic appearance of the lungs in chronic pulmonary emphysema is characteristic The lungs are pale, "anemic," and voluminous When the chest is opened, the overdistended lungs may be completely covering the heart and tend to bulge forward out of the open chest cavity instead of collapsing when the anterior chest wall

is removed The chest cage itself appears to be fixed and inflexible The lungs have a peculiar soft feathery feel and also tend to pit on pressure Indentations, produced by pressure of the ribs, may be noted on the visceral pleural surfaces Adhesions to the parietal pleura, mediastinum, and diaphragm, are fairly common, as a result



Fig 3 —Bullous emphysema affecting all lobes

of old infection The diaphragm is flattened or depressed and has a stretched "functionless" appearance

Subpleural blebs may be observed protruding above the surface of the surrounding lung, and others may be detected in the gross specimen by palpation (Fig 3) Found more commonly along the anterior margins, at the apices, and at the bases, the poorly supported regions of the lungs, these blebs and larger bullae range up to several centimeters in diameter Extensive inflammatory changes may be

found in the mucosa and walls of the bronchi and bronchioles The terminal bronchioles and the alveolar ducts are usually dilated. Some of these passages may be completely obstructed or even obliterated

The changes in the bony thorax vary according to the underlying cause of the pulmonary emphysema Generalized enlargement, particularly in the anteroposterior diameter, is most common. The angle of Louis may be very prominent The intercostal spaces are widened and the ribs lie horizontally rather than obliquely as is normal

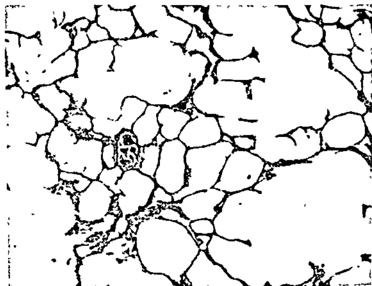


FIG 4—Low power view ×150 of moderately severe emphysema of the lungs showing thinning, rupture and coalescence of alveolar walls (Phloxine-methylene blue stain)

Calcification of the costal cartilages may be present Kyphosis of the thoracic spine and an unusually elevated position of the clavicles may be found In general, the chest lies in the position usually found only with inspiration

The histologic appearance will be mentioned briefly Changes observed within the alveoli range from simple dilatation and distortion, by thinning of the septa, to fragmentation and atrophy, depending upon the underlying cause of the pulmonary emphysema Through

sappearance of some of the interalveolar septa, there are large air paces composed of the remains of two or more of the alveoli (Fig 4)
Upon rupture of an alveolar wall, the ends undergo fibrosis, become idened and assume club shapes Clubbing usually indicates severe emphysema (Fig 5)
The general microscopic appearance has been likened to delicate lace Blebs, bullae, and air cysts are scattered among areas of atelectasis, bronchiectasis, and bronchopneumonia Varying degrees of arteriosclerosis and obliteration of the pulmonary arterioles and capil-

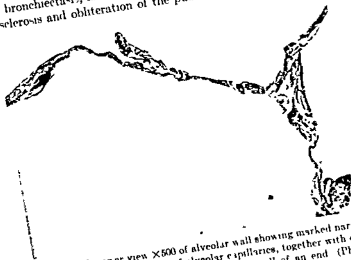


Fig. 5 —High power view ×500 of alveolar wall showing marked narrowing with apparent complete collapse of alveolar capillaries, together with characteristic rupture of an alveolar wall, and "clubbing" of an end (Phloxine methylene blue stain)

laries are evidence of pulmonary hypertension Special stains for elastic fibers may demonstrate the disappearance of these structures to a certain degree

Changes characteristic of the underlying cause of the chronic pulmonary emphysema are often evident If tuberculosis, sarcoidosis, or one of the pneumoconioses was the inciting agent, enlarged, calcified, or anthracosilicotic hilar nodes and fibrotic parenchymal changes may be noted When chronic pulmonary emphysema is secondary to bronchial asthma of long standing, the changes characteristic of

this disease will be present, comprising hyaline thickening of the basement membrane of the medium-sized bronchi, hypertrophy of the muscles of the medium-sized bronchi, eosinophilic infiltrations, mucous plugs in large and small bronchi, and excessive production of mucus and widening of the mouths of the bronchial glands

The anatomic changes of chronic cor pulmonale (hypertrophy and dilatation of the right ventricle), with or without evidence of congestive heart failure, are usually found in the final stages of chronic pulmonary emphysema. These changes are generally associated with the arteriosclerotic changes in the pulmonary arterioles and capillaries previously described

CHAPTER III

Pulmonary Function Tests in Chronic Pulmonary Emphysema

I. Introduction

The interpretation of pulmonary function tests and their specific application in chronic pulmonary emphysema will be discussed in detail in this chapter The actual techniques of these tests, however, are described in the Appendix, where they are available for immediate reference Until recently, pulmonary function tests were considered merely a tool in pulmonary research, with their practical application limited primarily to the evaluation of patients for thoracic surgery Their scope has expanded farther and farther afield to include the interpretation of new syndromes, especially when the tests

are supplemented by data obtained from cardiac catheterization Pulmonary and circulatory physiopathology should be evaluated together, and it has been the task of this combined approach to integrate such findings As a logical outcome, better understanding of the disturbed mechanisms has also aided in formulating proper treatment, particularly in the carbon dioxide intoxication syndrome and cor pulmonale (Chapters V and VI).

Although pulmonary function studies have become an integral part of the evaluation of patients with pulmonary disability, it is important to realize that these studies are *physiologic* tests, and that in many instances they do not indicate *where* or *what* the lesion is. Moreover, the lesion has to be large enough to disturb function sufficiently so as to cause definite changes beyond the normal range Such studies should be used only as a complement to information obtained from the detailed history, physical examination, roentgenological studies and other laboratory tests At times it is possible to detect physiologic disturbances in the absence of demonstrable abnormality by physical examination or roentgenographic studies

Pulmonary function studies are an *objective* measure of respiratory performance, and can be helpful in following the course of the disease or the effect of the treatment. By determining which functions are disturbed in a particular disease, plus the extent of their derangement and their response to treatment under experimental and clinical circumstances, we can obtain a clearer concept of the physiopathology of the disease process [83]

II. Terminology

Before proceeding with the discussion and interpretation of pulmonary function tests commonly employed on patients with chronic pulmonary emphysema we will review the new terminology recently recommended by a committee of respiratory physiologists (Fig 6).[119]

Tidal Volume is the volume of air moving in and out of the respiratory apparatus during resting inspiration or expiration

Vital Capacity is the maximal volume of gas that can be expelled from the lungs by forceful effort following a maximal inspiration

Inspiratory Capacity (complemental or complementary air) is the maximal volume of gas that can be inspired following a quiet expiration (measured from the resting end-expiratory level or *midposition*).

Inspiratory reserve volume (complemental or complementary air, complemental air minus tidal air, inspiratory capacity minus tidal volume) is the maximal amount of gas that can be inspired from the end-inspiratory position following a quiet inspiration (measured from the resting end-inspiratory level)

Expiratory reserve volume (reserve or supplemental air) is the maximal volume of gas that can be expired following a quiet expiration

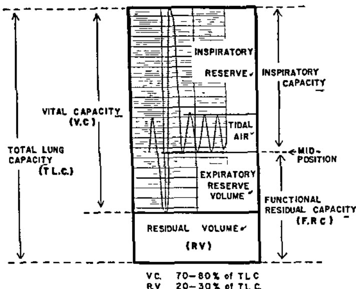


FIG 6 —Terminology used in pulmonary function studies

Functional residual capacity (functional residual air, subtidal volume, equilibrium capacity, normal capacity, mid-capacity) is the volume of gas remaining in the lungs at the end of quiet expiration

Residual volume (residual capacity, residual air) is the volume of gas remaining in the lungs at the end of a maximal expiration, in other words, it is the volume difference between the functional residual capacity and the expiratory reserve volume

Total lung capacity is the sum of the vital capacity and residual volume, in other words, it is the maximal amount of gas that can be contained in the lungs when they are fully expanded (Fig 6)

III. Cardiopulmonary Function Studies

A Lung Volumes

1 Tidal Volume

The tidal volume varies considerably even in normal subjects It is difficult to attach significance to changes in the tidal volume except when it is considered in conjunction with the respiratory rate, the product of these two factors constitutes the minute ventilation When the tidal volume becomes extremely small, nearly approaching the dead-space volume, the efficiency of ventilation is greatly impaired Shallow respiration, however, is rarely seen in patients with chronic pulmonary emphysema They generally hyperventilate until the final break in compensation results in hypoventilation This hyperventilation is accomplished by an increase of the tidal volume and of the respiratory rate (see under Minute Ventilation).

The average respiratory dead space measures about 125 cc to 150 cc in males and about 110 cc in females With advancing age, there is slight increase of this dead space to about 170 cc. The increase in dead space is probably a result of the increased residual volume The patient with emphysema who has his chest in a high inspiratory position and has a large residual volume will increase the dead space slightly, by about 20 cc His maximum respiratory dead space is about 200 cc

2 Vital Capacity

Vital capacity is the measurement of the difference between two *static volumes* of the lung, those of maximum inflation and maximum deflation Vital capacity measurements vary slightly at various times in the same normal subject The vital capacity of normals may vary as much as 20 per cent from the mean or calculated normal value.

The vital capacity is usually decreased when the lung volume is encroached upon by pulmonary or extrapulmonary factors such as surgical resection of lung tissue, atelectasis, edema, infection, fibrosis, limitation of chest expansion or diaphragmatic descent, pneumothorax and pleural effusion Thus, a decreased vital capacity does not in itself indicate the presence or type of pulmonary disease

The vital capacity may be *normal* in the presence of pulmonary

disability, many patients with chronic pulmonary emphysema have a normal or high vital capacity. Nevertheless, repeated vital capacity determinations in the same individual are important for evaluating spontaneous changes or the effect of treatment. This is particularly true when bronchial obstruction is present and the effect on the patient of various bronchodilator drugs is under observation.

Time—Vital Capacity Relationship. The vital capacity gains significance when the time relationship is considered as well. Normally, the volume of air exhaled in the first second should be at least 80 per cent of the total vital capacity.[65] The changes in this relationship during the treatment of bronchial asthma and pulmonary emphysema have been noted by many observers.[11, 41, 58, 85, 131] When these time relationship studies are applied to patients with bronchoconstriction, especially those with large vital capacities, it will be seen that the vital capacities are performed over a long period of time; there is prolongation of expiration. It has been observed bronchoscopically, in patients with pulmonary emphysema and bronchial asthma, that the bronchial walls collapse during expiration, especially with forceful expiration. In the patients with emphysema, this can be explained on the basis of a progressive increase in alveolar volume without a corresponding increase in the size of the air passages. At the onset of expiration, an increase results in resistance to expiratory flow. This mechanism inhibits complete emptying of the lungs, or allows complete emptying only by means of prolonged expiratory time.[124] (See Chapter II.)

The vital capacities of the patients with chronic pulmonary emphysema studied in our laboratory ranged between 1,160 cc. and 6,266 cc. with an average volume of 2,826 cc. However, when calculated as the sum of inspiratory capacity and expiratory reserve volume, the vital capacities ranged between 1,444 cc. and 6,552 cc., with an average volume of 2,860 cc. The latter constituted 77 per cent of the predicted normal vital capacity and 42 per cent of the average total lung capacity (6,694 cc.). The normal value of the ratio of vital capacity to total lung capacity is 59 per cent or more (Table 1).

Treatment of these patients with intravenous aminophyllin or bronchodilator aerosols demonstrated that the defects are not irreversibly fixed. The administration of 0.5 Gm. of aminophyllin intravenously produced an average improvement of 21 per cent of the

vital capacity. Similar improvement was obtained from 6 inhalations of a potent bronchodilator aerosol[83] (Table 2)

TABLE 1.—*Normal Lung Volumes and Findings in Patients with Chronic Pulmonary Emphysema*

	Normal Values	Pulmonary Emphysema
Vital Capacity		
Range (cc)	3120–4070*	1160–6266
Average (cc)	3610*	2826
Per cent of predicted	100 (B)	77
$\frac{\text{V C}}{\text{T L C}} \times 100$	>65 (H)	42
$\frac{\text{Inspiratory Capacity}}{\text{Vital Capacity}} \times 100$	72 (G)	66
$\frac{\text{Expiratory Reserve Volume}}{\text{Vital Capacity}} \times 100$	28 (G)	34
Functional Residual Capacity (cc)	3400 (G)	4829
Residual Volume (cc)	2430 (G)	3868
Total Lung Capacity		
Average (cc)	5920 (G)	6694
Per cent of predicted	100 (B)	125
$\frac{\text{Residual Volume}}{\text{Total Lung Capacity}} \times 100$	30 8 (C) 40 9 (G)	58

* Predicted normal values for the patients of this study
(B) Baldwin[8]
(G) Greifenstein[75] (over 50 years of age)
(H) Hurtado[86]

3 *Inspiratory Capacity and Expiratory Reserve Volume*

In chronic pulmonary emphysema, the chest is held in a high inspiratory position, such patients, accordingly, have a small inspiratory capacity but a relatively or absolute large expiratory reserve volume. In 1932, Lippelt[101] showed that, when normal subjects

breathed through a narrowed tube of a respirator, to simulate bronchial obstruction in expiration, an upward shift of the mid-position occurred, i.e., an increase in the functional residual capacity, with a simultaneous decrease in inspiratory capacity

In our patients with emphysema we found the expiratory reserve volume to be 34 per cent of the vital capacity (normal 20-28 per cent), and the inspiratory capacity 66 per cent of the vital capacity (normal 72-80 per cent), indicating an upward shift of the mid-position

TABLE 2 —*Average Percentage Improvement in Patients with Chronic Pulmonary Emphysema after a Single Treatment with Intravenous Aminophyllin, 0 5 Gm or 6 Inhalations of a Bronchodilator Aerosol*

	Aminophyllin	Bronchodilator Aerosols
Vital Capacity	+21	+22
Inspiratory Capacity × 100	−3	+6
Residual Volume	−9	−8
Total Lung Capacity	−0 6	−1 4
$\frac{\text{Residual Volume}}{\text{Total Lung Capacity}} \times 100$	−8 5	−7 6
Resting Ventilation	+5	+4
Maximal Breathing Capacity	+25	+59
Index of Mixing	−30	−34
Number of Patients	20	10

(Table 1) After the administration of intravenous aminophyllin, the ratio of inspiratory capacity to vital capacity was 63 per cent, after bronchodilator aerosols, 72 per cent, which represents changes of −3 and +6 per cent respectively (Table 2).

4 Residual Volume and Functional Residual Capacity

An increase in the residual volume indicates hyperinflation of the lungs Hyperinflation occurs from: (a) structural changes—diminished

elasticity, tearing of alveolar septa and decreased pulmonary capillary bed, characterizing true pulmonary emphysema, (b) airway obstruction – bronchial asthma, pulmonary emphysema, and tumors, (c) compensatory overinflation after pulmonary resection, (d) certain chest deformities—kyphoscoliosis and funnel chest, (e) progressive loss of pulmonary elasticity in advancing age, and (f) a variety of pulmonary disorders including congestive heart failure, and certain types of pulmonary fibrosis [88]

By itself, hyperinflation does not cause pulmonary disability This can be observed in many old people who have a normal total lung capacity, an increased residual volume and a residual volume/total lung capacity ratio, and yet have no respiratory difficulties A small residual volume will be seen with diffuse pulmonary fibrosis, or when numerous alveoli are collapsed or occluded Usually when the functional residual capacity is enlarged the residual volume is enlarged as well, and *vice versa* However, in the presence of a very small or very large expiratory reserve volume the one may be abnormal while the other is not affected

As a rule, patients with pulmonary emphysema have an enlarged functional residual capacity, we found this volume to average 4,829 cc. in our patients Normal subjects over 50 years of age have an average functional residual capacity of 3,100 cc.[75] Although many patients have a normal or even larger than normal expiratory reserve volume, an enlarged residual volume is usually found in emphysema; we noted an average value of 3,868 cc in our patients The normal value was observed to be 2,430 cc [75] (See Table 1)

There was only slight improvement of the residual volume with treatment After the administration of Aminophyllin and bronchodilator aerosols the residual volume decreased 9 and 8 per cent respectively (Table 2).

5 *Total Lung Capacity*

The total lung capacity is the sum of the residual volume and the vital capacity Normal values in subjects over 50 years of age averaged 5,920 cc [75] In diffuse pulmonary fibrosis the total lung capacity is usually decreased It is also decreased when lung tissue is replaced or compressed by a space-occupying lesion, congestion, fluid, or air and

compensatory hyperinflation does not occur in the remaining lung tissue The total lung capacity may also be decreased in the presence of large cysts, if they do not communicate with the bronchial tree, but will be normal or increased if they communicate freely [9] The total lung capacity is usually increased in chronic pulmonary emphysema, even in the presence of a small vital capacity

Patients with chronic pulmonary emphysema studied in our laboratory had an average total lung capacity of 6,694 cc, or 125 per cent of the predicted normal value (Table 1) Intravenous aminophyllin or bronchodilator aerosols did not change the total lung capacity significantly, it decreased an average of 0 6 and 1 4 per cent respectively (Table 2)

6 *Ratio of Residual Volume to Total Lung Capacity*

Since the absolute value of either residual volume or total lung capacity do not indicate normalcy, and since the residual volume bears a definite relationship to the total lung capacity, varying somewhat with age, this ratio of residual volume to total lung capacity is of great significance in the study of pulmonary disease The normal values for this ratio in various age groups are 20 0 per cent for 16–34 years, 23 4 per cent for 35–49 years, and 30 8 per cent for 50–69 years [6] Greifenstein *et al* [74] found this ratio to be 40 9 per cent in normal subjects over 50 An increased ratio is considered to be a reliable indicator of the *presence and degree of emphysema* [86] However, the *severity* of emphysema should be judged rather by the status of the arterial blood gases.[8] The ratio of residual volume to total lung capacity in our patients averaged 58 per cent (Table 1)

Treatment with intravenous aminophyllin or bronchodilator aerosols effected slight improvement in some of these values Treatment effected a downward shift in mid-position of the chest, an increase of the expiratory reserve volume and consequently, a decreased functional residual capacity and residual volume The total lung capacity remained essentially unchanged hence, the ratio of residual volume to total lung capacity also improved after treatment, 8 5 per cent after the administration of aminophyllin and 7 6 per cent after bronchodilator aerosols (Table 2).

Summary

The lung volume measurements of our chronic pulmonary emphysematous patients revealed the following: a usually decreased vital capacity as well as an abnormal time-vital capacity relationship, a small inspiratory capacity, an enlarged functional residual capacity and residual volume, a slight increase of the total lung capacity, and a significantly increased ratio of the residual volume to total lung capacity

B. *Ventilation Studies*

Pulmonary ventilation refers to the movement of air in and out of the lungs, and is evaluated as a volume-time measurement. Under physiologic conditions, pulmonary ventilation varies from minimal values during rest and sleep to maximal values during and after exhausting exercise The former is expressed as the *resting minute ventilation*, the latter as the *maximal breathing capacity*, and the difference between the two is the *ventilatory reserve*.

1. *Minute Ventilation*

An increase of resting ventilation is commonly observed in patients with pulmonary fibrosis or obstructive emphysema.[88] The mechanism for this altered function is not well understood, however. Partial airway obstruction may give either an increase or a decrease in respiratory minute volume, but severe obstruction usually is followed by a decrease.[173] It has also been demonstrated that an increase in oxygen in the inspired air at sea level will cause hypoventilation in anoxic patients, and on the other hand a decrease in oxygen will cause hyperventilation.

A possible homeostatic role of hyperventilation has been suggested by Motley *et al*, who found that hyperventilation decreases the "aeration gradient" (*i e*, the progressive difference in oxygen content of air at various levels of the respiratory tract) in patients with pulmonary fibrosis and emphysema.[115] In other words, resting ventilation increases in order to maintain normal gas exchange However, when the ratio of residual volume to total lung capacity is higher than 45 per cent, hyperventilation is no longer sufficient to maintain normal gas exchange [116] The minute ventilation in such patients is also

increased above normal levels during exercise These values are best expressed as L/min/M² of body surface area

The resting ventilation obtained in our patients with emphysema ranged between 4 60 and 9 95 L/min/M² of body surface area and averaged 6 30 L, which is approximately double the normal values obtained by Baldwin[6] (Table 3)

TABLE 3 —*Normal Ventilation Values and Findings in Patients with Chronic Pulmonary Emphysema*

	Normal Values	Pulmonary Emphysema
Resting Ventilation (L/min/M²)		
Average	M) 3 6 F) 3 2 (B)	6 3
Range		4 6–9 95
Maximal Breathing Capacity (L/min)		
Average	M) 167 1 ± 13% (Gy) F) 115 8 ± 18%	
	M) 68 8 ± 27 8 (G) F) 76 7 ± 25 0	36 2
Range		22 1–103 6
Per cent of predicted	100 (B)	42 6
Ventilatory Reserve at Rest (%)		
Average	>95	81 9
Range		64–95
Air Velocity Index		
Average	1 0	0 65
Range		0 41–0 85
Index Intrapulmonary Mixing ($\%N_2$)		
Average	<2 5 (C) <3 0 (G)	6 89
Range		2 29–11 29

(B) Baldwin [6]
(C) Cournand [47]
(G) Greifenstein [25]
(Gy) Gray [24]

The administration of aminophyllin or bronchodilator aerosols was generally followed by further hyperventilation, the resting ventilation increased 5 and 4 per cent respectively (Table 2)

2 *Maximal Breathing Capacity*

Maximal breathing capacity (M B C.) is the maximal displacement of air in and out of the lungs within a definite period of time It depends on many factors, particularly the age and body surface area Other factors also influence the M B C. performance, such as the size of the pulmonary bellows, the muscular force available, the degree of pulmonary elasticity, the resistance to air flow and the neuromuscular co-ordination The average in normal adults is approximately 150 L./min

Matheson *et al*[109] introduced experimentally an increase in air flow resistance, and observed a marked reduction of the M.B C. but no significant changes in the vital capacity. Performance of maximal breathing capacity depends on the ability of the patient to develop high air flow velocities Proctor *et al*[124] demonstrated that patients with pulmonary disease are unable to produce high air flow velocities The pathologic changes of the bronchial tree cause air turbulence and air flow velocities of only 20–30 L./min Increased tissue viscosity of the lungs as well as decreased elasticity also interferes with the development of high air flow velocities

The maximal breathing capacity is diminished in the presence of bronchoconstriction, as in bronchial asthma[83] and chronic pulmonary emphysema The M B C may be normal in pulmonary fibrosis, when uncomplicated by bronchial obstruction or decreased elasticity. An M B C which increases more than 10 per cent after the use of bronchodilator drugs indicates the presence of reversible bronchoconstriction

In our patients with chronic pulmonary emphysema, the maximal breathing capacity ranged from 22 1 to 103 6 L./min. Expressed in per cent of the predicted normal value, the maximal breathing capacity averaged 42 6 per cent (Table 3) It is evident from the considerable improvement of the M.B C obtained with a single dose of an effective bronchodilator drug that a large reversible factor is present in such patients The average improvement of the maximal breathing capacity was 25 per cent after an intravenous injection of Aminophyllin, and 59 per cent after bronchodilator aerosols (Table 2)

3 *Ventilatory Reserve*

An increase in physical activity requires an increase of ventilation above the resting ventilation values. The extent of impairment of

ventilatory function may be expressed by the ventilatory reserve: the difference between resting ventilation and maximal breathing capacity A decrease in ventilatory reserve results from either an increased resting ventilation or a decreased maximal breathing capacity

The reserve will be greater than 95 per cent in normal people at rest, when it is less than 70 per cent, severe exertional dyspnea exists [34] In our patients the reserve ranged from 64 to 95 per cent, averaging 81.9 per cent in our emphysematous patients (Table 3).

4 *Ventilation Equivalent*

Increased ventilation can be of two types: 1) metabolic—where the increased pulmonary ventilation results from an increased metabolic rate, as with exercise and hyperthyroidism, and 2) compensatory—where the increased pulmonary ventilation is out of proportion to the metabolic rate The latter is seen in certain pulmonary diseases The difference between these two types is determined by the *ventilation equivalent* This is the number of liters of air that are ventilated in order to consume 100 cc of oxygen The ventilation equivalent is normal in metabolic hyperventilation, but it is increased in compensatory hyperventilation The normal values for the ventilation equivalent range between 2 2 and 2 5 liters

5 *Air Velocity Index* (A V I.)

The vital capacity and maximal breathing capacity are both measures of lung volumes The maximal breathing capacity, however, is a better indicator of the presence of partial bronchial obstruction Gaensler suggested a formula to obtain more valuable information from these two tests The percentage of the predicted maximal breathing capacity, divided by the percentage of the predicted vital capacity, is expressed as the air velocity index (A V I) [67] The normal subject has an air velocity index of 1 0 The index is less than 1.0 in patients with significant bronchoconstriction, and is greater than 1 0 in those with loss of functioning lung tissue [67]

In our patients with chronic pulmonary emphysema the air velocity index ranged between 0 41 and 0 85, and averaged 0 65 (Table 3) This index should not be interpreted without the absolute values from

which it is derived, since a proportionate decrease in both maximal breathing capacity and vital capacity will result in a normal index of 1 0

6 Intrapulmonary Mixing

Effective alveolar ventilation depends on the even distribution of the tidal air to the normally perfused alveoli. This will result in a normal respiratory gas exchange. In healthy individuals, the tidal air diffuses readily and mixes with the residual volume, and equal aeration of the alveoli takes place. Effective ventilation will be impaired when the residual volume is abnormally large, the airways to the alveoli are inadequate, or the elasticity of one area is less than that of other areas This will result in an abnormal nitrogen-emptying *rate* from the lungs, at the end of a given period (7 minutes) of breathing 100 per cent oxygen, the alveolar air will still contain more than the normal amount of nitrogen (more than 2 5 per cent) At times, however, in the presence of effective hyperventilation a normal index of intrapulmonary mixing may be obtained, despite the presence of an abnormal residual volume

As a rule, a high index will be found in severe chronic pulmonary emphysema, but it may also be present in other types of pulmonary overinflation An abnormal index may likewise be found in patients with bronchial asthma,[83] bronchiectasis, congestive heart failure and the like Even though the index may be high, such patients do not necessarily show arterial hypoxia An effective mechanism has been demonstrated for redirecting pulmonary arterial blood flow away from unaerated toward aerated sections of the lungs, thus maintaining adequate arterial oxygenation despite the presence of poorly ventilated alveoli [48]

The index of intrapulmonary mixing in our patients with chronic pulmonary emphysema ranged from 2 29 to 11.29 per cent, with an average value of 6 89 per cent (Table 3). Some of the factors which influence intrapulmonary mixing are obviously amenable to treatment. The index decreased 39 per cent toward normal levels after intravenous Aminophyllin, and 34 per cent after bronchodilator aerosols (Table 2)

7 Instantaneous Air Flow Measurements

With the pneumotachograph, peak flows of single maximal expiratory and inspiratory efforts can be recorded and measured The effects of increased expiratory resistance on air flow velocities have been recorded in normal subjects and in patients with pulmonary disease[97, 124, 143] When a normal subject breathes through expiratory resistance produced experimentally, the following deviations from the normal pneumotachogram were observed[143]

a) The inspiratory curve showed an increase in amplitude but a decrease in per cent of the total respiratory cycle time.

b) The expiratory curve was dampened, the rise to maximum flow was delayed, and there was a sudden change in flow velocity, at the end of the cycle, instead of a smooth gradual return to the zero line. Similar pneumotachograms were obtained in studies of asthamatic subjects Nearly rectangular curves, with considerable dampening, and a rapid return to zero were characteristic of inelastic tissue or bronchial resistance.

Summary

Ventilation studies in our patients with chronic pulmonary emphysema revealed serious ventilatory defects in most of them, particularly the following: increased resting ventilation, decreased maximal breathing capacity, resulting in a markedly diminished ventilatory reserve, elevation of the index of intrapulmonary mixing, and lowering of the air velocity index below 1.0

C. Bronchospirometry

The pulmonary function studies thus far described have been concerned with measuring the total function of both lungs At times, however, it is essential to know the performance of each lung separately Bronchospirometry can measure lung volumes, ventilation and gas exchange for each lung separately but simultaneously Such methods may indicate whether one side is affected to a greater extent than the other By measuring the oxygen uptake of each lung, the relative circulation may also be evaluated. Cardiac catheterization

performed simultaneously with the latter determination permits a more exact evaluation of the circulation of each lung. Normally the right lung performs 55 to 65 per cent of the combined lung functions.

Bronchospirometry is helpful in evaluating the risk of pulmonary resection in patients with chronic pulmonary emphysema or those with tuberculosis, showing secondary emphysema. Patients with chronic pulmonary emphysema with one or more large blebs, bronchiectasis, or an abscess should not be subjected to pulmonary resection, unless the rest of the lung tissue has sufficient reserve for the postoperative period as well as for the distant future. Bronchospirometry has recently been extensively reviewed by Gaensler *et al*[5].

D. *Arterial Blood Studies*

The basic function of ventilation is to provide effective gas exchange (oxygen and carbon dioxide) between the circulation and the atmosphere. Abnormalities in pulmonary function may have a direct influence on the circulation and the arterial blood gases. For this reason, analysis of the arterial blood has become an important part of the evaluation of the pulmonary function. In normal subjects the oxygen saturation is greater than 96 per cent, and increases slightly after exercise, the carbon dioxide tension is usually below 42 mm Hg, and the pH ranges from 7.38 to 7.42.

The abnormalities of the arterial blood of patients with chronic pulmonary emphysema have been studied intensively by several groups of investigators[8, 8]. While arterial blood analyses may be normal in the patients with mild pulmonary emphysema, they become abnormal as the condition itself becomes more severe. Hypoxia occurs earlier in the course of the disease, inasmuch as carbon dioxide has a much greater diffusibility and is easily blown off. At first, hypoxia develops only after exercise, but later on, at rest as well. When severe hypoxia is present, carbon dioxide retention may also occur. A normal pH can be maintained for a long time by compensatory mechanisms, but eventually severe respiratory acidosis ensues. (See Chapter V.)

In a study of 68 patients with chronic pulmonary emphysema, oxygen saturation at rest ranged from 82.0 to 95.0 per cent, and after exercise from 75.6 to 94.8 per cent, for the severe to mild cases re-

spectively The carbon dioxide tension at rest ranged from 39 6 to 58 7 mm Hg, and after exercise from 40 0 to 62 4 mm Hg The pH ranged from 7 35 to 7 43 at rest, and from 7 32 to 7 41 after exercise [8]

Summary

Arterial blood studies may not reveal any abnormalities in patients with mild or moderately chronic pulmonary emphysema Hypoxia is noted only after exercise, but later on as the disease progresses, occurs at rest as well In the final stages of the disease, there is observed a rise in pCO_2 Respiratory acidosis is also commonly seen in this stage

E Cardiac Catheterization

In recent years the heart and the pulmonary circulation have been studied intensively, by the valuable technique of catheterization [46, 41, 112] This procedure is helpful in interpreting pulmonary disturbances, since not only does the circulation through the lungs affect the gas exchange, but abnormalities of ventilation also affect the pulmonary arterioles and the heart. Through cardiac catheterization it is possible to measure the pressures in the right heart, pulmonary artery and pulmonary capillaries, and to determine the cardiac output and the pulmonary arteriolar resistance (The normal values will be found in the Appendix)

The pulmonary vascular bed, in contrast to the systemic circulation, is a system of low resistance and low pressures The pressures in the pulmonary artery are 25 mm Hg systolic, 8 mm Hg diastolic, and the mean pressure is 15 mm Hg, the pulmonary "capillary" pressure is 10 mm Hg [49, 62]

Patients with advanced pulmonary emphysema frequently have pulmonary arterial hypertension The earliest sign of cor pulmonale in patients with severe chronic pulmonary emphysema is a rise in pulmonary arterial pressure Zimmerman studied 15 patients with cor pulmonale without congestive failure [174] The average pulmonary artery systolic pressure was 50 mm Hg, and the diastolic pressure was 22 4 mm Hg When congestive failure developed, the pressures rose higher Three such patients showed an average pressure of 66 mm

Hg systolic and 39 mm Hg diastolic in the pulmonary artery The cardiac output of these patients is also considerably increased, sometimes to 10 or more liters per minute [61]

In addition, the pulmonary vascular bed possesses a remarkable distensibility It has been demonstrated in normal subjects that the cardiac output can increase several fold without a concomitant increase in pulmonary arterial pressure and with only a slight increase in the arteriovenous oxygen difference [85, 130] In patients with advanced pulmonary emphysema, the pulmonary arterial pressure rises considerably with exercise from an already elevated resting level.

The *effects of hypoxia upon the pulmonary circulation have* been studied in normal subjects as well as in patients with chronic pulmonary emphysema (see Chapter VI) These defects are partially reversible by the use of procedures which improve ventilation and relieve the hypoxia

IV. Correlation of Pulmonary Function Studies

At this point we shall consider the function of the lung from three main aspects (1) ventilation, (2) perfusion, and (3) diffusion. The latter is the mechanism which connects ventilation and perfusion.[39] Normal diffusion requires maximal contact of the alveolar air and capillary blood, with good ventilation on one side of the alveolar membrane and good perfusion on the other, (Fig 7a). Impairment of this mechanism at any point will result in abnormalities of the blood gases (alveolar respiratory insufficiency).[131]

Ventilation-perfusion relationships may be disturbed by an increase in dead space ventilation, or venous admixture of the arterial blood In each of these situations the peripheral arterial blood will show hypoxia.

Dead Space Ventilation Part of the tidal volume is wasted in the actual dead space of the mouth, pharynx, trachea and major bronchi, where no gas exchange takes place (*anatomical dead space*). In addition, in severe chronic pulmonary emphysema there are many alveoli which are adequately ventilated but poorly perfused Thus the dead space ventilation is increased and the effective alveolar ventilation is decreased (physiologic dead space) (Fig. 7c). Under these circumstances the dead space ventilation will constitute more than 30 per

cent of the effective alveolar ventilation, this percentage is considered the upper limit of normal

Venous Admixture: A small amount of blood returning from the bronchial, Thebesian and other veins enters directly into the peripheral arterial blood This is a normal right-to-left shunt, causing

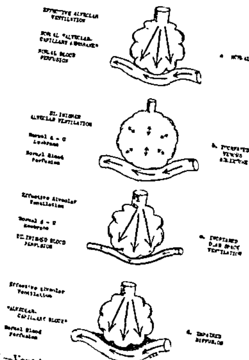


Fig 7 —Ventilation, perfusion and diffusion relationships

venous admixture of the arterial blood Normally, this amount of venous admixture is less than 6 per cent of the cardiac output In pulmonary disease, however, there are many segments of the lung with ineffective ventilation but with normal blood perfusion Obviously, the blood will return from these alveolar capillaries unoxygenated and will *increase the venous admixture* (Fig 7b)

Diffusion The alveolocapillary membrane consists of much more than just the lining cells of the alveoli and capillaries It consists of all the elements that establish a physiologic or anatomic barrier between the gas in the alveoli and the hemoglobin in the red blood cell,[100] namely: the alveolar membrane, the capillary endothelium, the wall and contents of the red blood cell, the plasma and lymph of the extracellular fluid, connective tissue, nerve and elastic fibrils A gradient of pressure is required for the oxygen molecule to reach the hemoglobin, this is the alveolar-arterial ("A-A") oxygen pressure gradient The normal values for this gradient are 9 mm Hg at rest and 16 mm Hg after exercise.[100]

The obstacles for the oxygen molecule in reaching the hemoglobin are increased by the addition of such elements as edema fluid, cellular exudates, granulomatous, fibrinous and collagen changes Under these circumstances the "A-A" gradient will increase in value. The "alveolar-capillary block" syndrome occurs with impairment of the process of pure diffusion (Fig 7*d*). The "A-A" gradient may also be increased as a consequence of abnormal ventilation–perfusion relationships The latter appears to be the case in most patients with chronic pulmonary emphysema [116]

Summary

Complete cardiopulmonary function studies in patients with chronic pulmonary emphysema show the following defects at various stages of the disease. (a) impaired ventilation, (b) abnormal perfusion and perhaps diffusion also, (c) poor gas exchange with or without respiratory acidosis, (d) pulmonary arterial hypertension and (e) cor pulmonale, with or without failure.

These studies also demonstrate to what extent many of these defects are reversible by treatment aiming to relieve bronchial obstruction and to improve ventilation and gas exchange. The correction of these abnormalities may decrease the pulmonary hypertension and prevent development of irreversible cardiac failure.

V. Physiologic Classification of Chronic Pulmonary Emphysema

Particularly valuable studies have been reported on the divergence between the histologic and the more recent physiologic concepts of

pulmonary emphysema based on lung volume measurements, gas exchange, and circulatory studies made possible by cardiac catheterization in Baldwin *et al* classified emphysema into four groups, on the basis of the levels of oxygen and carbon dioxide in the arterial blood, at rest and after exercise After standard exercise the following volumes were obtained:

In Group I, the arterial oxygen saturation was above 92 per cent, in Group II, the oxygen saturation was below 92 per cent and the carbon dioxide tension was below 48 mm Hg, in Group III, the oxygen saturation was below 92 per cent and the carbon dioxide tension was above 48 mm Hg Patients in the first three groups have uncomplicated pulmonary emphysema, in contrast to those in Group IV who have combined cardiopulmonary involvement

As the patient with chronic pulmonary emphysema passes from a mild stage (Group I) to the severest stage (Group IV), a progressively severe ventilatory insufficiency develops Alveolar respiratory insufficiency probably begins during the stage of Group II, and becomes more severe in Group III Patients in Group IV suffer, in addition, from cardiopulmonary insufficiency

The oxygen consumption is decreased during exercise in Group II, and to a greater degree in Groups III and IV The arterial oxygen saturation may improve during exercise in Group I, but it decreases in Group II and even more markedly so in Groups III and IV The arterial CO_2 tension is normal during rest and exercise in Groups I and II In Groups III and IV the CO_2 tension is elevated at rest, and increases during exercise The pH decreases during exercise in Groups III and IV, it may be below normal at rest in Group IV's

Since one or more of these groups may merge together, we consider it advisable to classify into three stages the clinical and physiologic manifestations of chronic pulmonary emphysema, as well as its management First, Intermediate, and Final

1 Physiologic Changes in the First Stage of Chronic Pulmonary Emphysema

Coughing, wheezing, and shortness of breath are usually present in the first stage of the disease, when most of the physiologic difficulties are centered about various degrees of ventilatory insufficiency These manifestations are related to the loss of effective alveolar

ventilation, secondary to air flow resistance and failure of the bucket-handle relationships of the lower ribs and diaphragm. The dyspnea in these patients is associated with a reduction in breathing reserve. The vital capacity (static function) may be low, normal, or even increased However, the time-vital capacity relationship is abnormal The patient requires a considerably longer time to complete the total vital capacity effort, he demonstrates inadequate expiratory emptying during the first and second seconds of the vital capacity effort

The total lung capacity increases, whereas the maximal breathing capacity (stress-dynamic function) decreases. Evidence of poor mixing and distribution of air within the alveoli is found in the elevate index of intrapulmonary mixing Spirograms reveal successive new mid-positions at the end of each expiration, thus demonstrating trapping of air, particularly during rapid breathing. Decreased pulmonary elasticity results in a state of hyperinflation, and the resting position of the lung at the end of quiet expiration approaches the inspiratory position This will lead in time to a high residual volume and to an increased ratio of the residual volume to total lung capacity. At this stage the patient compensates by hyperventilation, thus maintaining adequate alveolar ventilation and normal gas exchange, thus preventing the development of arterial hypoxia

2. Physiologic Changes in the Intermediate Stage of Chronic Pulmonary Emphysema

With repeated bouts of respiratory infection and bronchospastic crises, there is evidence of further impairment of gas exchange, with various degrees of arterial hypoxia and hypercapnia Progressively the arterial oxygen saturation may drop below 92 per cent and the arterial CO_2 tension may rise above 48 mm. of mercury. These abnormalities may be noted in particular after the standard exercise test In this stage, an increased alveolar-arterial oxygen pressur gradient ("A-A" gradient) is commonly found.

3 Physiologic Changes in the Final Stage of Chronic Pulmonary Emphysema

The degree of pulmonary insufficiency described thus far has been pointed out to be the result of inadequate alveolar ventilation or per-

fusion, leading to an imbalance of ventilation-perfusion relationships (distribution factor), and the main clinical manifestations are secondary to the arterial hypoxia and hypercapnia[64, 116]. As the degree of arterial hypoxia becomes more pronounced (arterial oxygen saturation below 80 per cent) the homeostatic mechanisms are further broken down. Compensatory hyperventilation is largely lost in this group. Respiratory acidosis and definite pulmonocardiac changes follow.

VS

CHAPTER IV
Clinical Concepts

I. Signs and Symptoms

The clinical manifestations of chronic pulmonary emphysema depend on the degree of pulmonary insufficiency present They range from simple disturbances in ventilation such as wheezing, shortness of breath on exertion, and coughing, through chronic hypoxia and carbon dioxide retention, to chronic cor pulmonale with heart failure Many patients do not survive the intermediate stage It must always be remembered that dyspnea, cough, wheezing, and cyanosis are common signs and symptoms in many pulmonary and cardiac diseases, and often make the differential diagnosis difficult.

The first manifestations are commonly cough and shortness of breath, with no apparent correlation between the occurrence of dyspnea and the development of a barrel-shaped chest Hypercapnia may not be subjectively troublesome in the early stages The patient is usually not dyspneic, or only slightly so, when resting or sleeping At this stage he is generally able to sleep in a normal recumbent position, or even flat on his back The dyspnea may be brought on or become accentuated during exertion, or after coughing or sneezing paroxysms, or while straining, singing, or shouting, procedures in which an increase of the intrapulmonary pressure occurs In this stage dyspnea usually subsides on rest The progressive increase in severity of the dyspnea parallels the reduction in the patient's breathing reserve There is also some evidence suggesting that the dyspnea may be accentuated by the Hering-Breuer reflex from the overdistended lungs and by reflexes from the distended pulmonary arteries

The patient's dyspnea may actually be simple hyperventilation as part of the compensatory mechanism for achieving more effective alveolar ventilation and elimination of carbon dioxide. Exertional dyspnea and orthopnea in the later stages are associated with arterial hypoxia and hypercapnia. Some of the dyspnea, particularly in the advanced cases of fibrosis, is the product of fixation of the tracheobronchial tree, in normal individuals, the tracheobronchial tree is always in a state of dynamic motion.

Bronchospastic crises, resembling paroxysms of bronchial asthma, with wheezing and prolongation of expiration, are usually secondary to accumulated secretions or bronchial infections. Sibilant wheezes and rhonchi may sometimes be absent even though expiration is prolonged. Frequent upper respiratory infections, sinobronchitic involvement and industrial and allergenic exposures contribute further to the progressive cough, dyspnea and bouts of wheezing. Recurring bronchitis, often due to mild infections, may initiate functional disability in the early stages of the disease in patients previously able to get about fairly well in spite of a limited respiratory reserve.

The character of the cough depends largely on the underlying disorder responsible for the bronchitis, at first it is likely to be short, hacking, paroxysmal and usually unproductive. It is thus type of cough that at a later stage may cause "explosive blowouts" of bronchiolar and alveolar walls. The cough that is productive is better tolerated and the underlying bronchoconstriction more readily relieved. Coughing varies with the time of day, and is usually more pronounced during the early waking or sleeping hours. It may vary with the seasons and with changes in posture. In acute bronchitis secondary to irritation, the sputum is usually scanty, mucoid, and tenacious, but may become blood-streaked during severe paroxysms of unproductive coughing. In the bronchitis that becomes chronic, the quantity of the sputum increases and the cough becomes more effective. The sputum may be the purulent yellow of infection, or it may be gray or black due to dust, smoke, soot or similar mechanical irritants. The sputum may originate from the paranasal and sinus regions, as well as from the bronchi. Copious expectoration, especially after coughing or changes in position, suggests bronchiectasis or lung abscess. In such cases the sputum tends to be foul, in uncomplicated chronic pulmonary emphysema, the mucoid or mucopurulent sputum is usually sweet-tasting.

Coughing may result from infections, allergic involvement, nonspecific mechanical irritations, or from reflexes affecting the upper respiratory passages The upper respiratory passages are particularly susceptible to infection The chronic inflammatory changes of sinobronchitic disease and chronic bronchitis are the most common causes of cough in patients with chronic pulmonary emphysema Adenoidal hypertrophy and infection, nasal polyps and paranasal sinus disease are frequently related to the troublesome cough observed in patients with allergic bronchitis. The secretions drip down the posterior pharynx onto the larynx and bronchi causing annoying cough during early sleeping or early waking hours Acute bronchial irritation by dusts, gases, vapors, fumes, or foreign bodies, usually excites a severe spasmodic cough The mechanical effects of cold air, wind, dusty atmosphere, tobacco smoke, or excessive shouting or talking usually start the cough Sudden exposure to cold produces a type of paroxysmal bronchoconstriction that may be essentially reflex in nature, the receptors presumably lying somewhere in the upper respiratory passages The reflex apparently precipitates paroxysmal wheezing and a hacking cough leading eventually to the production of viscid white sputum.

This reflex pattern may itself be stimulated by cough Cough may be originally a response to the inhalation of tobacco smoke for example, and coughing may bring about reflex bronchoconstriction, thus self-perpetuating the cough for a matter of minutes Enlarged and chronically inflamed tonsils or an abnormally long uvula occasionally may be responsible for the nonproductive type. Secondary distressing symptoms that may follow in the wake of cough are physical and mental exhaustion, headaches, insomnia, pain or soreness in the lower part of the chest or in the abdomen, herniae, and loss of urinary bladder sphincter control in women The coughing "habit" unfortunately seems to persist in some patients after the cause has been removed Fatigue, weakness, anorexia, indigestion, flatulence, constipation, and weight loss are common, and the patient may acquire the typical "chronic appearance". The gastrointestinal symptoms may be connected with the hypoxia and hypercapnia noted in the later stages of the disease.

Syncope may follow a severe or continuous coughing paroxysm. This is the so-called "post-tussive syncope". It is most likely the

same syndrome that Charcot described many years ago in La Salpetrière as "laryngeal epilepsy." A series of coughs greatly increases the intrathoracic pressure—a Valsalva-like maneuver—the venous return is decreased, consequently the cardiac output diminishes to the point of not supplying sufficient cerebral blood flow and unconsciousness may follow (see Chapter VI).

On physical examination of the patient with chronic pulmonary emphysema, the lung fields are hyperresonant and the area of lung resonance is usually increased. Whispered and spoken sounds are less easily felt or heard, and the breath sounds are feeble or distant. The respiratory excursion of the chest may be reduced to one-half inch or even less. The distended thorax is held in the inspiratory position. Because of loss of elasticity, the lungs do not return to their normal midposition at the end of expiration. Movement of the diaphragm is poor. Expiration is prolonged and instead of being passive requires active effort. The ribs may be elevated and everted and the interspaces widened. The accessory muscles of respiration are active and the thoracic cage may move upward and slightly forward as a unit. The sternocleidomastoid muscles are generally prominent. The neck may appear short and thick. The chest may be long and narrow. Many of these patients present the so-called "barrel-shaped" chest. The thoracic spine may be kyphotic, the shoulders raised and thrown forward and the back rounded.

The respiratory movements commonly appear uncoordinated. The breath sounds are usually "dampened." Inspiration is short and the inspiratory breath sounds harsh. Rhonchi and sibilant rales are generally present. Moist rales may be elicited if there is concurrent infection, partial atelectasis, bronchiectasis, or congestive failure. The heart sounds are usually normal, but may be poorly elicited because of the overdistended lung. The cardiac impulse is generally not visible. Heart murmurs are particularly apt to be overlooked. The area of cardiac dullness is usually diminished or even absent. Liver dullness can be elicited lower than normal. Clubbing of the fingers and cyanosis have been noted in advanced cases. As further evidence of peripheral hypoxia, the axillary and pubic hair may become sparse, and the skin more atrophic and delicate, suggesting a feminine appearance. Clinically this resembles in many ways the appearance of some patients with chronic Laennec's cirrhosis of the liver.

II. Psychosomatic Aspects of Dyspnea

An abnormal breathing pattern is a common and disconcerting occurrence There may be dyspnea without hyperpnea as well as hyperpnea without dyspnea. The physician should determine whether the breathing disturbance is organic or functional. Dyspnea in an emotionally disturbed person may persist even after medical reassurance because the automatic process of breathing is upset by self-awareness Dyspnea is by definition a purely subjective feeling and as such cannot be too well correlated with objective measurements It must be admitted that these symptoms are so often confusing that the physician is unable to distinguish between the somatic and psychic components Three possible mechanisms can be defined and will be taken up separately

A *Dyspnea Inducing Emotional Reactions.* This can occur in patients with either functional or organic lung disease The response of the subject to the effects of hypoxia, such as at high altitudes, is one of the best examples of this process of critical self-consciousness The normal subject may find himself sighing frequently, taking deep irregular breaths and becoming aware of the subjective discomfort of increased respiration These manifestations are particularly noted after the slightest exertion or after heavy meals Disturbing emotional effects may be noted even by healthy and mentally well-adjusted individuals, and even in subjects who are aware of the physiologic effects of altitude, there is a sense of annoyance at least, and often a tendency to suspect the basic integrity of the pulmonary and circulatory apparatus

The process of aging imposes physiologic limitations on the breathing capacity The subject is often confused in attempting to discern whether his difficulties denote organic disease or are premonitory of the declining period of life

B *Dyspnea Resulting from Neurotic Drives* Sighing respiration and irregular breathing patterns, or hysterical hyperventilation, noted in neurotic patients or those with hyperthyroidism, may represent the initial trigger mechanism in the production of dyspnea Once established, the dyspnea serves to increase the patient's disturbance A vicious cycle is thus established.

C *Dyspnea Associated with Primary Emotional Disturbances:* In

this group, the emotional component plays a definite role in the etiology or in the clinical evolution of the lung disease. This appears to be especially true in many cases of chronic bronchial asthma and, therefore, often in emphysema. It is not our purpose to enter into a discussion of psychosomatic disturbances as etiologic factors in chronic pulmonary emphysema except to note their common occurrence and their definite influence on the clinical course. In many patients with chronic pulmonary emphysema we have noted profound emotional disturbances directly related to their difficulty in breathing. Specifically these are emotional disturbances that arise from physical incapacity, not mental changes due to functional or organic brain disease. These patients have to live with a disease that restricts physical activity without actually threatening life, and the psychologic trauma at times overwhelms them. The chronic hypoxia that may be present in these patients for many years can by itself, also lead to changes in personality of a more progressive and irreparable nature.

Thus, an analysis of the many factors involved in the development of chronic pulmonary emphysema cannot be considered complete, nor management of the case adequate, without an understanding of the patient's emotional status. The psychologic reorientation necessary to lessen the unbearable fear of invalidism is more readily achieved during the earlier phases of the disease. Many physicians have repeatedly noted that certain patients failed to improve despite most appropriate physiologic therapy. The psychologic component in chronic illness is now clearly recognized and is included in the rational treatment of such patients. Too often, unfortunately, an awareness of these factors comes in the later stages of pulmonary decompensation when it is unlikely that any medication or procedure will change the status of the patient from that of a bedridden invalid.

The actual value of psychotherapy in preventing physiopathologic changes in the lungs is unknown. It should be evaluated concurrently with the clinical, roentgenologic, and pulmonary function tests and interpreted in the light of repercussions of changing mood attitudes on the autonomic nervous system and hypothalamic-pituitary-adrenal axis. Whatever its possibilities in reversing the progression of the disease, psychotherapy may help the patient adjust more readily to his degree of incapacity. With successful psychotherapeutic reorien-

tation, his "therapeutic threshold" may be lowered Moreover, his more rational concept of therapeutic aids will reduce them from "indispensable crutches" or "shrines" to their exact physiologic equivalents Psychotherapy should not be imposed on every patient exhibiting emotional disturbances Unless the patient is personally convinced of his need for such therapy and fully agrees to it, he cannot benefit by it The following case summary of one of our patients presents several of the features just discussed.

A 57-year-old married man was referred to us for study, because of progressive respiratory disability He gave a history of mild and intermittent bronchial asthma "since being gassed" in World War I, which had increased in severity during the past ten years The physical findings were those of an obese male, whose significant abnormalities were confined to the lung He had multiple rhonchi, wheezes typical of emphysema and impairment of pulmonary function, these remained constant during the year of study The vital capacity was fixed at about 2,400 cc, and the maximal breathing capacity at about 35 L/min The slightest exertion made him obviously short of breath

Outwardly cheerful, he was an extremely friendly man, pink-cheeked, bold, a fluent talker, with a warm laugh and courteous manner

His jolly manner was only superficial, however, for he readily admitted discouragement and easily broke into tears There seemed to be many problems disturbing him, both old and new

He was one of a family of twelve children All of them, the patient in particular, had worshipped the father He had vivid memories of playing baseball and poker with his father, exchanging jokes with him, and laughing his way through childhood in a very close and harmonious family unit

News of the death of his father was received by the patient while he was convalescing in an army hospital after a gas attack in World War I The coincidence of that loss, which the patient still could not refer to without choking up with tears, may have had an influence on his respiratory disease Other events may have been contributory The patient married a nagging, domineering woman older than himself, and this led to a stormy marriage At first he was away from home much of the time, working unusually hard as a field engineer He subsequently obtained a civil service position in a large city Here his domestic tension rapidly increased, reaching a crisis that coincided with the onset of severe and intractable asthma

Regardless of any speculative psychomatic factors in the precipitation of his illness, the major emotional upheaval at the time he came for treatment was clear-cut *his reaction to the drastic limitations of his breathing* This man, once extremely active, able to work sixteen to twenty hours a day with a gang on bridges and dams could not walk across the street without gasping for breath

Although he tried to keep up a cheerful front, he admitted that he felt as though he were in prison He spoke of how ashamed he was when he had to

stop for breath on the street, and of how he felt that everyone was looking at him and thinking he was a freak. "It's like you're walking around on the bottom of the ocean with not enough oxygen coming down to you." He embraced each new therapeutic procedure with enthusiasm and was enormously discouraged when it failed to bring lasting relief. He felt, with some justice, that his superiors were writing him off as a nice fellow, but one too physically handicapped for promotion to a job involving more responsibility. Psychologically, he needed physical activity, yet he was forced to restrict himself more and more. Periods of rest at home inevitably exposed him to the constant nagging of a hypercritical wife, often precipitating asthmatic seizures. He longed for physical work, yet that outlet was becoming increasingly unattainable. He remarked that he wished he could "die and get it over with."

The changing attitude of enthusiasm and discouragement is fairly typical of most emphysematous patients. Like many others, unfortunately, this patient was directed to psychotherapy too late. Although his emotional status had significantly improved, the pulmonary changes were too far advanced for parallel improvement. Management of this patient had to be directed at trying to get him to accept his restrictions and rehabilitate himself in quiet interests, and so find consolation in what for him had come to mean a living death.

III. Complications

Certain changes which occur during, or are associated with the course of chronic pulmonary emphysema, may be best defined as sequelae rather than complications. Bronchial obstruction may lead to localized obstructive emphysema. Reabsorption of trapped gas in such an area often leads to atelectasis. Atelectatic border zones observed in roentgenograms are probably due to compression of adjacent lung tissue by expanded emphysematous areas. Bronchiectatic changes frequently develop in areas of atelectasis. Bronchiectasis is also common in chronic pulmonary emphysema, secondary to chronic paranasal sinus disease, bronchitis, and bronchial asthma. Areas of recurrent pneumonitis with resultant fibrotic scarring may also be observed in chronic pulmonary emphysema.

On the other hand, the occurrence of acute mediastinal emphysema or a spontaneous pneumothorax, although quite uncommon in chronic pulmonary emphysema, should be regarded as a real complication. Spontaneous pneumothorax usually occurs after rupture of a subpleural

emphysematous bleb or bulla Interstitial emphysema may develop after rupture of a more centrally located bleb or bulla or after rupture of a central bronchus or alveolus (see Chapter I); it may be localized or it may spread over or through the lung to the mediastinum, peritoneal and pleural cavities, and upward to the neck This train of events may also occur after avulsion of a mediastinal or pleural adhesion close to a bleb or bulla. The episode may be related to sudden effort involving the Valsalva maneuver, such as coughing, sneezing, straining at stool, shouting or lifting, or it may follow a sharp blow to the chest Such a blow need not be directly over the "blowout" area, for contrecoup effects may occur. Fortunately, the sudden changes in intrapulmonary pressure that occur in the Valsalva maneuver are usually evenly distributed. Sudden localized overdistention, however, may be followed by a spontaneous pneumothorax (Fig 8)

A fairly common result of the chronic cough is the development of herniae through the weak abdominal wall. These are usually inguinal or femoral, but incisional, epigastric, or umbilical herniae are not rare Surgical repair of these herniae is often unsuccessful because of the continued cough The use of abdominal supports and trusses is the treatment of choice until the cough is controlled completely for a period long enough to insure that adequate healing will follow surgery. Other uncommon complications that may follow coughing paroxysms and cause considerable pain and discomfort, are fractured ribs (Fig 8), subluxation of a costochondral articulation, and rupture of muscle fibers.

In the later stages of chronic pulmonary emphysema, as arterial hypoxia and hypercapnia become more pronounced, respiratory acidosis, the carbon dioxide intoxication syndrome, pulmonary hypertension, pulmonary arteriosclerosis, chronic cor pulmonale and cardiac failure occur more commonly. These complications will be discussed in more detail in Chapters V and VI

IV. Radiologic and Fluoroscopic Studies

The chest roentgenogram and fluoroscopy are usually distinctive but not accurate indicators of the degree of physiologic insufficiency. Individual lung function can be evaluated to a certain extent by

fluoroscopy during quiet and deep breathing. This may reveal the presence of unilateral bronchoconstriction by visualization of localized trapping of air. Poor lung expansion may also be detected – due to pleural thickening, empyema, or space-occupying lesions

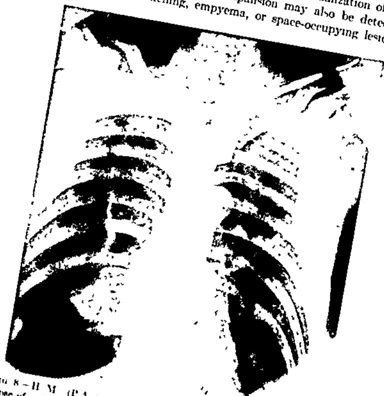


FIG. 8. – H. M. (P.A. view.) Spontaneous pneumothorax with 75 per cent collapse of right lung, bilateral bullous emphysema, old tuberculous scarring in right apex and old "cough" fracture of tenth rib posteriorly.

Bright or translucent lung fields (increased radiability) are due to hyperaeration (Fig. 9). In lateral films this may be noted particularly anteriorly in the wide chamber between the sternum and the heart and aorta, and posteriorly between the lower thoracic spine and

heart In some patients the sternum may actually bulge forward and the lung parenchyma extend in front of the heart down to the diaphragm (Fig 10) Films taken at the end of expiration may reveal an

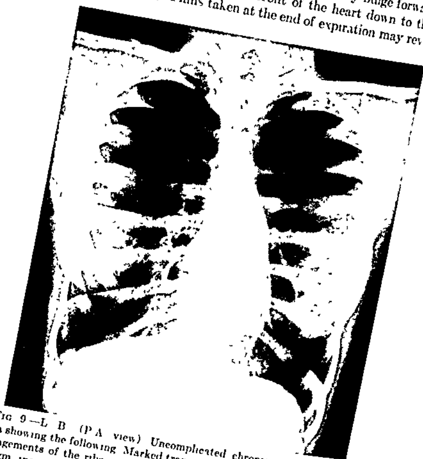


FIG 9—L B (P A view) Uncomplicated chronic pulmonary emphysema showing the following Marked transverse dilatation of chest, horizontal arrangements of the ribs with widened interspaces, lowered position of diaphragm, increased radiance throughout and droplet shaped heart

increased amount of air in contrast to the relatively airless appearance in normal subjects (Figs 11 and 12) The translucency may be limited to the bases of the lung when the emphysema is predominantly basal Translucency varies with the degree of radiographic penetra-

tion It should be kept in mind that fibrosis, polycythemia, increased viscosity, and congestive failure may mask the degree of radiability. The ribs lie more horizontal than usual (Fig 9), and calcification of

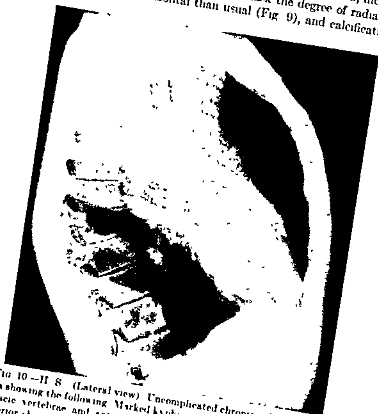


Fig 10 —H S (Lateral view) Uncomplicated chronic pulmonary emphysema showing the following Marked kyphosis with slight wedging of the mid thoracic vertebrae and anterior bulge of the sternum, wide anterior and posterior chambers due to interposition of emphysematous lung between the heart and sternum and the heart and spine respectively

the costal cartilages occasionally may be noted The bronchovascular markings and pulmonary fibrosis vary in density, depending on the degree of pulmonary hypertension and associated pulmonary diseases The pulmonary vessels are usually enlarged and the root shadows are

generally increased in size and density. Downward motion of the hilae may be noted on inspiration With associated pulmonary fibrosis of the upper lobes, the root shadows may be pulled upward above the third interspace anteriorly

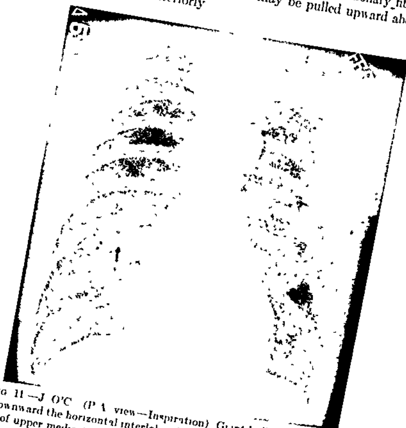


FIG 11 —J O'C (P A view—Inspiration) Giant bulla in R U L displacing downward the horizontal interlobar fissure (see arrow), moderate displacement of upper mediastinum to the left and old "cough" fracture of the sixth rib posteriorly on the right Note the virtual absence of lung markings in the R U L

Annular transparencies with absence of lung markings are due to subpleural blebs or bullae (Figs. 11 and 12) A thin line of increased density usually surrounds the area of rarefaction, within which lung markings are almost obliterated. The blebs are more commonly noted

in the poorly separated parts of the lung, along the anterior margins, at the apices, and at the bases Larger air cysts, with or without fluid

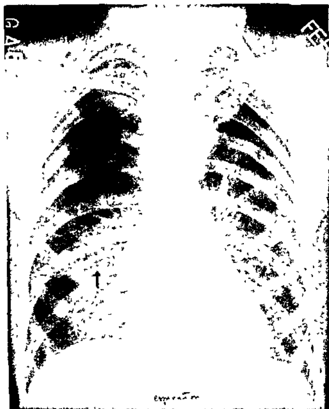


FIG 12 —J O'C (Same patient Fig 11 taken in expiration) No ventilation of R U L —trapped air Inspiration and expiration carried out only by the right middle and lower lobes as noted by change in the position of the diaphragm and horizontal interlobar fissure

levels, are less common These air cysts or pneumatoceles may become very large, their borders sharply defined by marginal atelectasis of the contiguous compressed lung (Fig 13) Inasmuch as they do not

generally increased in size and density Downward motion of the hilae may be noted on inspiration With associated pulmonary fibrosis of the upper lobes, the root shadows may be pulled upward above the third interspace anteriorly.

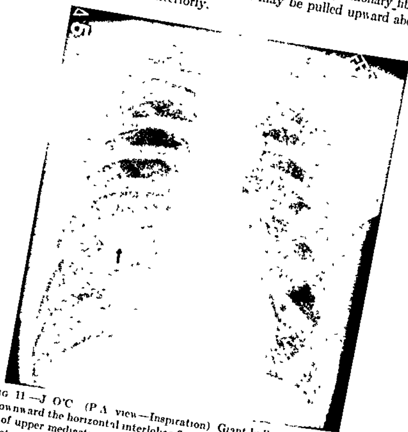


FIG 11 —J O'C (P A view—Inspiration) Giant bulla in R U L displacing downward the horizontal interlobar fissure (see arrow), moderate displacement of upper mediastinum to the left and old "cough" fracture of the sixth rib posteriorly on the right Note the virtual absence of lung markings in the R U L

Annular transparencies with absence of lung markings are due to subpleural blebs or bullae (Figs 11 and 12) A thin line of increased density usually surrounds the area of rarefaction, within which lung markings are almost obliterated The blebs are more commonly noted

in the poorly separated parts of the lung, along the anterior margins, at the apices, and at the bases Larger air cysts, with or without fluid



FIG 12—J O'C (Same patient Fig 11 taken in expiration) No ventilation of R U L—trapped air Inspiration and expiration carried out only by the right middle and lower lobes as noted by change in the position of the diaphragm and horizontal interlobar fissure

levels, are less common These air cysts or pneumatoceles may become very large, their borders sharply defined by marginal atelectasis of the contiguous compressed lung (Fig 13) Inasmuch as they do not

usually communicate with the bronchial tree, they are generally of no great clinical significance. They can be determined by bronchography, or by body section roentgenography These cysts can, however, cause mechanical compression when they are large enough, or become secondarily infected, or rupture to cause mediastinal emphysema or pneumothorax. They have also been found to extend through the anterior mediastinum into the opposite hemithorax Congenital air

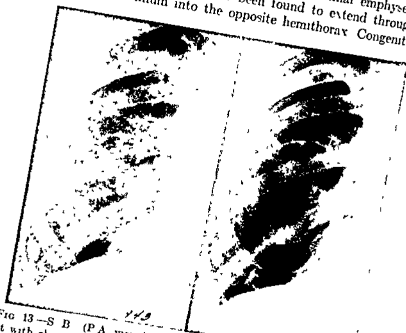


Fig 13—S B (P A views) Solitary pulmonary cyst in R L L in a patient with chronic pulmonary emphysema showing progressive enlargement over a period of 6 years Congenital bony bridge can be seen between the seventh and eighth ribs

cysts have a great tendency to communicate with the bronchi, and thus become secondarily infected As a result their walls become thicker The presence of bullae or cysts is not necessarily an indication of the severity of the emphysema Patchy areas of associated bronchiectasis and atelectasis may be observed, particularly in patients with bronchoconstriction who have not been adequately treated (alternating areas of emphysema and atelectasis).

The heart size is usually small It is frequently described as long and narrow in patients with uncomplicated pulmonary emphysema (Fig 9) Roentgenographic studies of the development of chronic cor pulmonale will be discussed in Chapter VI

The diaphragm generally assumes a flattened contour, may even appear depressed or reversed in its curvature, and usually moves very little, or on rare occasions, paradoxically The digitations of the muscular attachments of the diaphragm to the chest cage may be noted (Fig 28) *Restricted diaphragmatic motion is a good index of severe emphysema, particularly in the absence of bronchial asthma* Films taken at the end of inspiration and expiration confirm this observation The inspiratory sniff test, with mouth closed, may be helpful The normal response to two or more rapid, forceful sniffs, with mouth closed, is a series of quick and short diaphragmatic cusp descents An effective sniff, in the normal subject, usually decreases the intratracheal air pressure With cough, the diaphragmatic movement should be rapidly upward, caused by the increase in abdominal pressure and the closing of the glottis An effective cough in the normal subject usually increases the intrapulmonary air pressure, as in the Valsalva maneuver with the glottis closed These jerky motions are not usually observed in patients with chronic pulmonary emphysema The expiratory blow test ("blow the candle out") or ("blow against the palm of my hand") is also useful, and generally reveals the retarded expiratory airflow as well as the futility of attempts to get these patients to "blow harder and more rapidly"

Bronchography usually reveals evidence of bronchostenosis by the failure of the viscous contrast medium to fill the emphysematous area The appearance of this condition has been likened to a barren tree largely without leaves Alveolograms like those typical in normal subjects are not usually obtained In areas that have filled, the bronchial branches are often forced apart and distorted by the rearrangement of the bronchial tree, secondary to collapse of the overstretched alveoli and the loss of bronchial support In emphysema that is secondary to chronic bronchial asthma, widespread obliteration of the lumens of the bronchi of the third and fourth order may be observed Fleischner considers some kind of bronchial obstruction the primary cause of chronic pulmonary emphysema, and gives bronchographic x-ray evidence to support this [63] In normal subjects he has been able

to demonstrate shortening and narrowing of the bronchi during expiration, with heaping up of oil deposits and actual ridge formation from wall to wall, due to the redundant, loosely attached mucosa. Increased secretions in patients with bronchitis and asthma are responsible for the same type of expiratory obstruction, thus preventing proper expiratory emptying, and eventually may lead to the formation of the greatly dilated alveoli seen in chronic pulmonary emphysema.

Bronchography can be carried out with the use of a water-soluble contrast medium, like Umbradil. Although the contrast is believed to be less than that obtained with Lipiodol, it has the advantage of being more readily expelled, and thus the danger of allergic reactions may be minimized. By this method it is possible to differentiate three different stages in the bronchogram: a. bronchial filling, b. alveolar filling, and c. lymphovenous reabsorption. The normal time that elapses during the third phase is from thirty to forty-five minutes.[9]

The frequent development of bronchiectasis in emphysematous patients often raises the problem of excisional therapy. In these patients especially, total bronchograms are imperative. The disease is commonly diffuse and the benefits of local resection should be carefully evaluated. It is particularly important that the lingular segment is properly mapped out and found free of disease before attempting removal of the left lower lobe.

CHAPTER V

The Carbon Dioxide Intoxication Syndrome

I. Clinical Manifestations and Development

We have been increasingly aware of a clinical picture comprising mental changes, due to profound disturbances of the acid-base balance, which may progress even to coma the carbon dioxide intoxication syndrome The isolated finding in the blood of emphysematous patients, of high concentrations of carbon dioxide is commonly associated with the advanced stages of the disease We are concerned here with the complications that may arise when high arterial carbon dioxide levels are associated with the simultaneous development of decompensated respiratory acidosis The more advanced stages of the syndrome are further characterized by the presence of hypoventilation

This syndrome is most commonly observed in patients with chronic hypoxia of long standing, usually secondary to chronic pulmonary emphysema, with or without pulmonocardiac disease Yet it may also be seen where there is no lung disease, whenever respiratory depression is induced by drugs or diseases that affect the respiratory center Weakness, headache, lassitude, confusion, irritability, personality changes and air hunger may be noted More serious central nervous system manifestations may occur as the pH falls: depressions of respiration, coma, and even death.

In these patients, the elevated arterial pCO_2 (hypercapnia) is

usually associated with arterial hypoxia Both are direct evidence of defective gas exchange. Under normal conditions, at rest and at sea level, the rate of ventilation of the lungs appears to be governed by the level of carbon dioxide in the arterial blood. The latter exerts its controlling effect upon the respiratory minute volume by direct action upon the medullary respiratory centers—the so-called centrogenic drive for respiration [27] There is also a less sensitive controlling mechanism, normally inactive, comprising the chemoreceptors of the carotid and aortic bodies, innervated respectively by the ninth and tenth cranial nerves These organs are sensitive to decrease in arterial oxygen tension and also to gross changes in carbon dioxide levels, the so-called chemoreflex drive for respiration.

In the emphysematous patient in whom these control mechanisms remain normally active, hypercapnia leads to hyperventilation and the return of the carbon dioxide level toward normal. If hyperventilation does not succeed in producing effective alveolar ventilation, carbon dioxide retention persists with dulling of the respiratory center response to carbon dioxide (adaptation).[71] Some of the symptoms at this stage, such as headaches, lassitude, confusion, and irritability have been attributed to cerebral effects secondary to the high pCO_2,[36, 169] or to the simultaneous depression of pH.[18]

The sudden administration of high concentrations of oxygen in an attempt to relieve dyspnea and cyanosis may be followed by an increase in the distressing symptoms of this syndrome. In these patients, the medullary respiratory centers appear to have lost their sensitivity to the pCO_2 stimulus to so great an extent that the peripheral chemoreceptors in the carotid and aortic bodies have become mainly responsible for maintaining respiration, for they are the only known structures which are stimulated by hypoxia Sudden injudicious relief of hypoxia removes the stimulus which incites the sole homeostatic mechanism still sustaining respiration The patient responds with hypoventilation or even apnea Still greater increase may follow in arterial pCO_2 and CO_2 content, with an ultimate respiratory acidosis with a drop in arterial pH

The early stages of this syndrome are accompanied by a rise in the plasma carbon dioxide levels, but, due to a compensatory mechanism, there is little or no actual drop in pH This compensation is initially achieved by the action of the buffer systems of the blood Much more

significant, though slower in appearing, is the preferential excretion of chloride ions and retention of the sodium ions by the kidney.

As the syndrome progresses, particularly when it is suddenly aggravated by the injudicious administration of oxygen with a resulting hypoventilation, these compensatory mechanisms are overwhelmed. The precipitate rise in arterial pCO_2 results in a further drop of the plasma pH to the levels of decompensated respiratory acidosis. It is this respiratory acidosis which appears primarily responsible for drowsiness, delirium, coma and death. Recent studies have shown that cerebral oxygen consumption is impaired by a marked drop in the arterial pH[89, 90]. Unconsciousness will occur when the cerebral oxygen consumption drops below the critical level of 2.1 cc per 100 Gm. of brain tissue per minute (normal 3.3 cc. per 100 Gm. per minute). Cerebral blood flow and cerebral oxygen consumption are also decreased when the spinal fluid pressure reaches more than 450 mm. of water, but the spinal fluid pressure does not reach such high levels in the majority of patients with the carbon dioxide intoxication syndrome. Other possibilities have been suggested: cerebral vasospasm may be a direct consequence of the increased pO_2, increased pO_2 may also directly or reflexly cause cerebral depression.

This syndrome is more likely to occur if ventilation is further decreased by respiratory-depressing drugs such as morphine, barbiturates and anesthetic agents.

II. *Acid-Base Disturbances in Respiratory Diseases*

A. The need frequently arises for evaluating acid-base disturbances in patients with respiratory disease. Respiratory acidosis is by far the most common disturbance, but one may encounter all types of deviation, for there are usually associated metabolic changes, present as primary or secondary complications. Although the acid-base status should be determined from arterial blood, an anaerobically obtained sample of venous blood may be quite helpful, if the results are interpreted correctly. Simultaneous determination of the CO_2 content and pH is always necessary.

The possible disturbances of the acid-base balance can be divided into two main groups: respiratory and metabolic. The factors that indicate the degree of either are as follows: a) Respiratory disturb-

ances reflected essentially by the arterial partial pressure of carbon dioxide (pCO_2) expressed in mm Hg. The normal value is 40 mm Hg. This can be obtained directly by the Riley technique,[139] or indirectly from the Henderson-Hasselbach equation, when the pH and carbon dioxide content of the arterial blood plasma are known. These determinations are greatly facilitated by the use of the nomogram of Singer and Hastings.[149]

Acid-base changes due to respiratory disturbances can be followed accurately only by the arterial pCO_2; changes in CO_2 content are a much poorer guide. The CO_2-combining power is useless for evaluating the degree of respiratory involvement. The pCO_2 is rapidly altered by lung ventilation, and represents the primary factor in assessing these respiratory changes.

B. Metabolic disturbances are best assessed by the determination of whole blood buffer base (B_B^+), the sum of the buffer cation concentrations, expressed as milli-equivalents per liter of plasma (mEq/L). There are two types of anions: 1) the fixed acids (A^-) or nonbuffer anions like chloride, sulfate, lactate, etc., and 2) the buffer anions like bicarbonate, phosphate, protein, hemoglobin, etc. The total base (B^+) or the sum of all cations (sodium, potassium, calcium, magnesium, etc.), is essentially equal to the total anion concentration, since the pH is always close to neutrality. Of the total base (B^+), a certain amount is always reserved for neutralization of the fixed acid anions. The remainder of the total base, not utilized to neutralize fixed acid, is known as the buffer base (B_B^+), and is ordinarily neutralized by the blood buffer anions, largely bicarbonate.

The buffer base (B_B^+) changes are related to pure metabolic variations, mainly originating from such processes as intestinal absorption and secretion, renal function and tissue metabolism. The buffer base will be decreased if (B^+) decreases or if (A^-) increases; and it will be elevated under reverse circumstances. Normal values are 45–55 mEq/L.[149]

In several respects, the buffer base determination has advantages over the CO_2-combining power for the assessment of pure metabolic disturbances. The latter determination assumes that: 1) plasma CO_2 parallels the bicarbonates or alkali reserve, 2) other buffers are negligible in comparison to bicarbonates, and finally, but most important, 3) no respiratory involvement is present.

Buffer base is not determined directly, but can be obtained from the nomogram of Singer and Hastings.[149] Having determined the pCO_2, and the buffer base, the two so-called independent variables, one can recognize and understand the various types of disturbance of acid-base balance.[149] The disturbance is mostly commonly purely respiratory or metabolic at the outset, although a mixed type is also to be seen Nonetheless, even the pure disturbances become mixed,

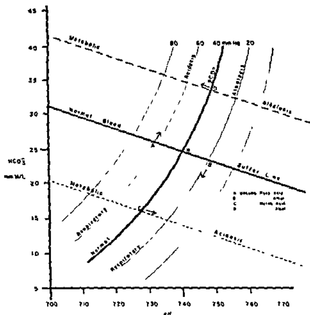


Fig 14 —Disturbances in acid-base balance

provided they persist long enough to call for compensatory mechanisms

Figure 14 based largely on Davenport's[49] concept, helps to visualize these changes graphically A, B, C and D represent four *pure* types of acid-base disturbances before any compensation takes place The sector below and above the normal blood buffer line indicates metabolic acidosis and alkalosis respectively, while the pCO_2 isobar of

40 mm. Hg separates respiratory acidosis on the left and respirato alkalosis on the right. The direction of the arrows indicates the pat that compensatory mechanisms will follow in order to restore the basi homeostatic mechanisms A patient in respiratory acidosis, (A), is fixed on a high pCO_2 level, has a low pH and high bicarbonate content In the process of compensation, a secondary metabolic alkalosis takes place, tending to minimize displacement of pH. Serum bicarbonates are further increased, along with excretion of chloride anions through the kidneys Other primary uncompensated disturbances can be seen in this figure, and are self-explanatory.

Combined primary changes in acid-base balance involving simultaneously the pCO_2 and buffer base are of a more complex nature, and must be evaluated with the additional help of the history and clinical course of the patient. Here again the need is emphasized for following the changes in both the pCO_2 and the buffer base, since the patterns of compensation may assume individual characteristics.

III. Treatment of the Carbon Dioxide Intoxication Syndrome

A. Preventive Measures

Since prevention is by far the best treatment, the following principles should be kept in mind:

1) The physician should always be on the lookout for the development of this syndrome during the management of patients with chronic hypoxia secondary to chronic pulmonary emphysema and pulmonocardiac disease

2) Oxygen concentration of over 50 per cent must be avoided in these patients

3) Large or repeated doses should not be employed of respiratory-depressing drugs (morphine, barbiturates, and depressing anesthetic agents) which may reduce the pulmonary ventilation

The zealous physician, affording relief from dyspnea with "adequate" sedation and "treating" hypoxia with high concentrations of oxygen, will encounter this syndrome all too frequently

B Oxygen Treatment in Patients with Carbon Dioxide Retention

This troublesome syndrome will not ordinarily occur if respiration is not further depressed by the use of respiratory-depressing drugs, and if *high concentrations of oxygen are not suddenly administered* to the chronically hypoxic patient Barach has stressed that these patients need a carefully graded program of oxygen therapy [18] One should employ a nasal catheter with humidified oxygen At the outset, flows of 1 liter per minute should be administered The flow may be increased by 1 liter each day or two, until 6 liters of oxygen per minute are administered. A concentration of 38 per cent oxygen in the inspired air can be obtained with this flow Some variations in the flow rates may be necessary from time to time There should also be a gradual daily reduction in oxygen concentrations at the conclusion of therapy, to permit the patient to readjust himself to normal atmospheric conditions Many patients do quite well on a home program of oxygen therapy administered before meals and at bedtime over periods of several weeks to months

A very gradual reduction in the total pulmonary ventilation may follow this therapy This slow change in ventilation permits the progressive development of further compensatory metabolic alkalosis, and prevents a sudden drop in arterial pH There will also be obobserved a gradual rise in arterial pCO_2 and CO_2 content However, following this rise the CO_2 levels may fall, as alveolar ventilation returns to normal The sensitivity of the medullary respiratory center to pCO_2 may be restored with a graded oxygen program

C Specific Treatment

The successful management of the carbon dioxide intoxication syndrome and its most serious sequela, decompensated respiratory acidosis, may require more than the judicious use of oxygen therapy When the syndrome actually appears and there is evidence of depressed respiration and decompensated respiratory acidosis, emergency treatment should center about the following added measures, which are listed by order of importance (For fuller discussion refer to their respective chapters)

1) The use of intermittent positive pressure breathing (Chapter XI).

2) Institution of an emergency pneumoperitoneum (Chapter XII).

3) The use of respiratory body chambers (Chapter XI)

As previously pointed out, morphine administration, alone or in combination with high concentrations of oxygen, may be responsible

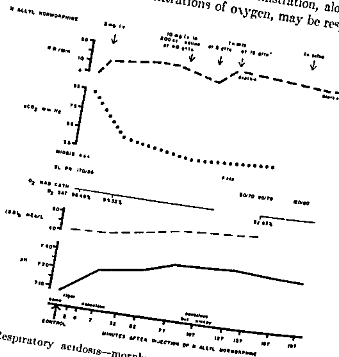


FIG 15 —Respiratory acidosis—morphine induced—N-allyl normorphine treated

for the development of respiratory depression and the carbon dioxide intoxication syndrome We have employed a morphine antagonist, N-allyl-normorphine (Nalline), in several such instances with gratifying results (Fig. 15) [55]

The summary of our findings in one of these patients appears in Fig 15 An 80-year-old woman was given 30 mg of morphine sulfate for the relief of pain caused by the incarceration of a femoral hernia.

Severe respiratory acidosis and coma followed shortly. Immediate and sustained improvement was noted after the intravenous administration of N-Allyl-Normorphine. A total dose of 25 mg was given over a period of 157 minutes. Following the improvement in the respiratory rate, it can be seen that there was a pronounced drop in the abnormally high pCO_2, and a progressive rise of the pH toward normal.

CHAPTER VI

Pulmonocardiac Complications

I. Development and Clinical Manifestations

Right ventricular hypertrophy and cor pulmonale can occur as a complication of a wide variety of pulmonovascular disorders Utilizing the classifications of Dexter[53] and Spain[153] we have listed the most frequent causes, arranged according to duration and anatomical localization of the primary lesion (Table 4). Among the chronic diseases of the lung, pulmonary emphysema is the most frequent cause of right ventricular hypertrophy.

The pulmonary vascular bed, already reduced in extent by the anatomic narrowing or actual obliteration of many of the pulmonary arterioles, is diminished even further as a result of hypoxia In addition polycythemia develops Thus the patient with chronic pulmonary emphysema has many abnormalities which contribute toward an increased cardiac output. The increased blood flow must pass in the lungs through a vascular bed restricted both anatomically and physiologically, leading to the development of progressive pulmonary arterial hypertension If this condition persists, pulmonary vascular sclerosis may appear, comparable in a way to the peripheral arteriolar sclerosis in systemic hypertension. Pulmonary arteriosclerosis was found at post-mortem in 75 per cent of patients with chronic pulmonary emphysema [116]

The early clinical manifestations of pulmonocardiac involvement are in essence the signs and symptoms of the underlying pulmonary emphysema previously described.

TABLE 4.—*Pulmonary Causes of Cor Pulmonale**

I) Acute
- Pulmonary embolism
- Pulmonary edema

II) Subacute
- A) Miliary carcinomatosis
  - 1) Hematogenous dissemination
  - 2) Lymphatic dissemination
- B) Acute miliary tuberculosis

III) Chronic
- A) Diffuse pulmonary parenchymal diseases
  - 1) Emphysema
    - a) Obstructive
      - i) CHRONIC PULMONARY EMPHYSEMA
      - ii) Acute bullous emphysema
    - b) Nonobstructive
      - i) Senile emphysema
      - ii) Kyphoscoliosis
      - iii) Compensatory emphysema
  - 2) Pulmonary fibrosis and granulomatosis
    - a) Bronchiolar
      Boeck's sarcoid, Pneumonoconiosis, Tuberculosis (repeated bronchogenic spreads with healing)
    - b) Interstitial
      Chronic interstitial fibrosis, Beryllium poisoning, Scleroderma, Interstitial emphysema
    - c) Intra-alveolar
      Beryllium poisoning, Diffuse adenomatosis
    - d) Pleural
      Chronic pyogenic or tuberculous emphysema, Hemothorax
- B) Diffuse pulmonary vascular disease
  - 1) Recurrent pulmonary embolism
  - 2) Thrombosis of pulmonary artery
  - 3) Sickle cell anemia
  - 4) Schistosomiasis
  - 5) Arteritis
    - a) Thromboangiitis obliterans
    - b) Lupus erythematosis disseminata
    - c) Polyarteritis nodosa
    - d) Raynaud's disease
    - e) Rheumatic arteritis
  - 6) Idiopathic

* Based on the Dexter[33] and Spain[133] classifications

The *early* diagnosis of chronic cor pulmonale can be confirmed only by finding (through cardiac catheterization) an elevated pressure in the pulmonary artery Changes in the electrocardiogram, roentgenogram, venous pressure, circulation time and rapid infusion test usually appear only when the disease is clinically well established. During this early phase frequently a compensatory hyperventilation may be noted, appearing in untoward episodes induced by bronchoconstriction, infection or exercise.

The *later* manifestations of pulmonocardiac complications are essentially those due to chronic pulmonary hypertension, hypertrophy, dilatation, failure of the right heart, and the superimposed effects of chronic hypoxia Cyanosis of the lips and finger tips and clubbing may develop, or become more pronounced An elevated blood carbonic anhydrase level has been observed in these patients, which catalyzes the conversion reaction of carbon dioxide to and from bicarbonates[2] This may compensate for the retarded carbon dioxide excretion in the lung

In patients with chronic pulmonary emphysema, normal or rapid values have been described for arm-to-tongue or arm-to-face circulation time A lengthened circulation time may be found where increases are observed in the intrapleural pressure[91, 93] The hypoxia, polycythemia and consequently hypervolemia are largely responsible for dilatation of the right ventricle. Cardiac dilatation is generally although not invariably associated with increased cardiac output, the next trigger mechanism may initiate failure This can occur as a result of exercise, respiratory infection or bronchiolar obstruction

The exact mechanism and pathway for the vasoconstriction that follows in the wake of hypoxia has not been clearly defined Inasmuch as the vasoconstriction can be somewhat reversed by correcting the hypoxia, the cardiopulmonary changes due to this factor may also be partially reversed. However, the changes due to anatomical narrowing cannot be reversed by correcting the hypoxia. This fact may be utilized to distinguish pulmonary hypertension of hypoxic origin from primary arteriolosclerosis of the pulmonary vascular bed

Elevation of the pulmonary arterial pressures observed by many investigators during hypoxia has been the subject of extensive research.[114, 170] Motley *et al*[114] clearly demonstrated the pulmonary hypertensive effect due to hypoxia in 5 unanesthetized human sub-

jects Dexter et al.[52] employed the term "pulmonary arteriolar resistance," referring to the site of resistance, namely, the precapillary area.

In the studies by Wescott et al.,[128] when hypoxia was induced by breathing 13 per cent oxygen, a significant rise of 24.6 per cent was observed in the mean pulmonary artery pressure, and of 48.5 per cent in the pulmonary arteriolar resistance. However, there was no significant change in the mean pulmonary "capillary" pressure, or for all practical purposes in the pulmonary venous pressure. These investigators concluded from their observations that hypoxic elevation of the pulmonary arteriolar resistance may be a contributory and reversible factor in the etiology of some types of pulmonary hypertension.

Dexter et al.[52] also made several other observations of fundamental importance on the basic circulatory disturbances in cor pulmonale. They stated that cor pulmonale and hypoxia could exist independently of one another. In cor pulmonale, the increased resistance in the pulmonary arterioles or minute arteries of the lung is the basic circulatory disturbance. Increase in pulmonary artery pressure will eventually be followed by right ventricular hypertrophy. At this point right ventricular failure is rare, and disability is apt to be due to the patient's underlying pulmonary disease, rather than to his circulatory disturbance. With occurrence of hypoxia severe enough to cause a drop in arterial oxygen saturation below 80 per cent, further changes were observed, particularly an increase in the cardiac output. However, when the pulmonary arteriolar resistance rose to three times the normal or higher, hypoxia produced an actual fall in the cardiac output. Apparently in such circumstances the overworked myocardium cannot deliver the required blood. At this stage, cardiac failure of serious significance unfortunately often occurs. The Dexter group noted that when hypoxia was corrected by the administration of oxygen, the cardiac output returned promptly to normal.[52] These investigators were not certain of the precise relationship between hypoxia and pulmonary arteriolar resistance.

These effects of chronic hypoxia should always be considered as a superimposed pathologic factor upon the underlying anatomical derangement. Most of the patients with chronic pulmonary emphysema who develop cor pulmonale have an associated diffuse fibrosis affect-

ing the pulmonary circulation by different mechanisms The fibrosis may be present in the pulmonary vasculature alone, or it may effect a circulatory blockade by involving the alveolar-capillary septa. Cor pulmonale, almost by definition, has been invariably bound to pure right ventricular hypertrophy. This concept should be revised, however, for it has recently been shown that in some instances the left ventricle and systemic circulation are likewise involved.

The careful studies of Liebow[99] and his associates demonstrated *the significance of shunts between the bronchial and pulmonary artery systems* These anastomoses, which compensate for the inadequate blood supply through the pulmonary artery branches, essentially represent a left-to-left shunt between the left ventricle and left auricle Left ventricular hypertrophy then develops, in order to maintain the increased output. In lung segments with pulmonary arterial blood flow still present, the anastomoses between the bronchial and pulmonary arteries may create a left-to-right shunt. Under these circumstances, the higher pressure of the systemic blood flow imposes an added resistance to the right ventricular output.

✓ The clinical manifestations in the advanced stage reveal easy fatigability, exertional dyspnea, orthopnea and cyanosis. There may be evidence of congestive failure: a tender or enlarged liver, distended neck veins, increased venous pressure, peripheral edema, ascites. The cardiac rhythm and blood pressure tend to remain unchanged if *the systemic circulation does not participate in* the pathological process The pulmonic second sound is accentuated, and is usually greater than the aortic second sound. The chest roentgenogram, fluoroscopy and the electrocardiogram generally reveal evidence of right *ventricular enlargement; the ability of the right ventricle to* hypertrophy in order to meet the increased load is most impressive ✓

When myocardial degeneration develops, or when the optimal stretch of the myocardial fibers has been exceeded, the increased cardiac output begins *to fall* Nevertheless, it *still may be* greater than normal, even in the presence of congestive failure. *Compensatory hyperventilation is largely lost in these patients, and hypoventilation is more common.* There has been observed in patients with severe degrees of arterial hypoxia a tendency toward respiratory acidosis, marked polycythemia and hypervolemia, severe pulmonary hypertension, high cardiac output with or without failure, and a marked elevation of diastolic pressure in the right ventricle[41, 170] In these

last stages the pulmonary hypertension is irreversible and is accompanied with intractable heart failure As a rule these patients never recover full compensation, and succumb in a few months

II. Electrocardiographic Findings

When the electrocardiographic pattern of right ventricular hypertrophy appears, it signifies either a pulmonary artery mean pressure of 30 mm mercury or higher, or a total pulmonary resistance exceeding 750 dynes/seconds/cm $^{-5}$, which is about three times the normal

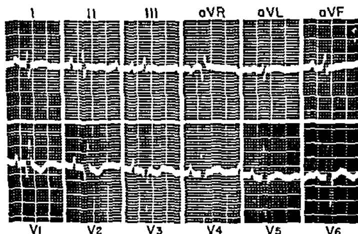


FIG 16 —Electrocardiogram in a patient with chronic cor pulmonale

(Fig 16)[53] However the absence of such a pattern does not rule out the existence of pulmonary arterial hypertension and cor pulmonale[53 87] The electrocardiographic criteria for diagnosis of right ventricular hypertrophy, according to Sokolow and Lyon,[152] are as follows (1) In the right precordial leads tall R and small-to-absent S waves, delayed ventricular activation time, depression of the TS-segments, inversion of the T waves, and an R/S ratio greater than 1 in V 1, (2) In the left precordial leads, small R and prominent S waves and an R/S ratio less than 1 in V 5 and V 6. In AVR there are prominent R waves[152]

The electrocardiographic position of the heart is usually vertical, with clockwise rotation. The axis may be perpendicular, due to simultaneous retrodisplacement of the apex. Very often, right bundle branch block is associated with right ventricular hypertrophy.



FIG 17—C G (P A view) Chronic cor pulmonale in pulmonary emphysema Note prominent pulmonary artery (arrow), left auricle and ventricle are not enlarged

III. *Roentgenologic Diagnosis*

Roentgenographically the diagnosis of cor pulmonale can be made when certain changes are noted. In the *early stages*, the enlargement of the oval density of the pulmonary trunk is best visualized in the

right anterior oblique position As the disease progresses, there will be noted an enlargement anteriorly of the pulmonary conus

In the *later stages*, in the postero-anterior view, the pulmonary artery will bulge below the aortic knob and its arc will be longer than normal. A notch will be noted below this bulge of the pulmonary



FIG 18—C G (Same patient Fig 17, lateral view) Enlarged right ventricle and pulmonary conus Note increased surface contact of right ventricle with sternum

artery, thus differentiating chronic cor pulmonale from mitral stenosis[109] (Fig 17) Furthermore, enlargement and increased pulsations of both hilar regions will confirm the diagnosis Esophagrams do not usually reveal any displacement of the esophagus

In the more *advanced stages* of the disease the right ventricle may be enlarged, thereby increasing the diaphragmatic surface of the

The electrocardiographic position of the heart is usually vertical, with *clockwise rotation. The axis may be perpendicular*, due to simultaneous retrodisplacement of the apex Very often, right bundle branch block is associated with right ventricular hypertrophy.

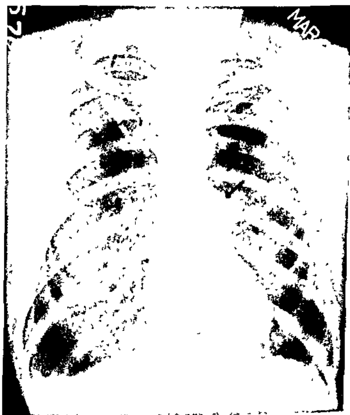


Fig 17 —C G (P A view) Chronic cor pulmonale in pulmonary emphysema Note prominent pulmonary artery (arrow), left auricle and ventricle are not enlarged

III. Roentgenologic Diagnosis

Roentgenographically the diagnosis of cor pulmonale can be made when certain changes are noted In the *early stages,* the enlargement of the oval density of the pulmonary trunk is best visualized in the

right anterior oblique position As the disease progresses, there will be noted an enlargement anteriorly of the pulmonary conus

In the *later stages*, in the postero-anterior view, the pulmonary artery will bulge below the aortic knob and its arc will be longer than normal A notch will be noted below this bulge of the pulmonary



FIG 18 —C G (Same patient Fig 17, lateral view) Enlarged right ventricle and pulmonary conus Note increased surface contact of right ventricle with sternum

artery, thus differentiating chronic cor pulmonale from mitral stenosis[108] (Fig 17) Furthermore, enlargement and increased pulsations of both hilar regions will confirm the diagnosis Esophagrams do not usually reveal any displacement of the esophagus

In the more *advanced stages* of the disease the right ventricle may be enlarged, thereby increasing the diaphragmatic surface of the

The electrocardiographic position of the heart is usually vertical, with clockwise rotation. The axis may be perpendicular, due to simultaneous retrodisplacement of the apex. Very often, right bundle branch block is associated with right ventricular hypertrophy



FIG 17—C G (P A view) Chronic cor pulmonale in pulmonary emphysema Note prominent pulmonary artery (arrow); left auricle and ventricle are not enlarged

III. Roentgenologic Diagnosis

Roentgenographically the diagnosis of cor pulmonale can be made when certain changes are noted In the *early stages*, the enlargement of the oval density of the pulmonary trunk is best visualized in the

right anterior oblique position As the disease progresses, there will be noted an enlargement anteriorly of the pulmonary conus

In the *later stages*, in the postero-anterior view, the pulmonary artery will bulge below the aortic knob and its arc will be longer than normal A notch will be noted below this bulge of the pulmonary



FIG 18 — C G (Same patient Fig 17, lateral view) Enlarged right ventricle and pulmonary conus Note increased surface contact of right ventricle with sternum

artery, thus differentiating chronic cor pulmonale from mitral stenosis[108] (Fig 17) Furthermore, enlargement and increased pulsations of both hilar regions will confirm the diagnosis Esophagrams do not usually reveal any displacement of the esophagus

In the more *advanced stages* of the disease the right ventricle may be enlarged, thereby increasing the diaphragmatic surface of the

The electrocardiographic position of the heart is usually vertical, with clockwise rotation The axis may be perpendicular, due to simultaneous retrodisplacement of the apex Very often, right bundle branch block is associated with right ventricular hypertrophy.

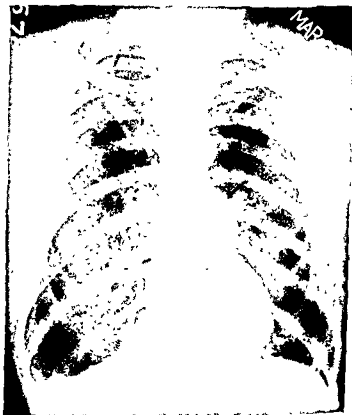


Fig 17—C. G (P A view) Chronic cor pulmonale in pulmonary emphysema Note prominent pulmonary artery (arrow), left auricle and ventricle are not enlarged

III. Roentgenologic Diagnosis

Roentgenographically the diagnosis of cor pulmonale can be made when certain changes are noted. In the *early stages*, the enlargement of the oval density of the pulmonary trunk is best visualized in the

right anterior oblique position As the disease progresses, there will be noted an enlargement anteriorly of the pulmonary conus

In the *later stages*, in the postero-anterior view, the pulmonary artery will bulge below the aortic knob and its arc will be longer than normal A notch will be noted below this bulge of the pulmonary



FIG 18—C G (Same patient Fig 17, lateral view) Enlarged right ventricle and pulmonary conus Note increased surface contact of right ventricle with sternum

artery, thus differentiating chronic cor pulmonale from mitral stenosis[108] (Fig 17) Furthermore, enlargement and increased pulsations of both hilar regions will confirm the diagnosis Esophagrams do not usually reveal any displacement of the esophagus

In the more *advanced stages* of the disease the right ventricle may be enlarged, thereby increasing the diaphragmatic surface of the

heart This can be seen most clearly in the right or left anterior oblique positions[193] Increased surface contact of the right ventricle with the sternum is best seen in the right lateral position (Fig 18).

At times the presence of emphysema makes it difficult to determine the size of the heart chambers In the presence of associated wasting diseases (pulmonary tuberculosis or silicosis), the heart may appear small even though the right ventricle is hypertrophied However, by contrast visualization of the cardiac chambers and great vessels in patients with emphysema, some degree of enlargement of the right ventricle or the pulmonary artery has been noted in almost all of the cases.[156]

IV. Treatment

A. General

The management of this group of seriously ill patients warrants a greater optimism, if one bears in mind that the physiological changes which have been described are largely reversible in most instances, albeit only temporarily The dominant abnormality, hypoxia, must be corrected, since it is fundamentally responsible for the previously outlined sequence of events This can be effected through vigorous use of measures to relieve bronchoconstriction, by employing bronchodilator aerosols (with or without intermittent positive-pressure breathing), Ephedrine or Orthoxine orally, and Aminophyllin orally, rectally or intravenously. Antibiotics should be administered for upper or lower respiratory tract infections, parenterally or by the aerosol route These infections may initiate an episode of acute hypoxia superimposed on the chronic hypoxia, thus producing a sudden break in cardiac compensation. Hypoxia should be corrected through the use of low concentrations of oxygen to avoid the dangerous sequelae of the carbon dioxide intoxication syndrome Improvement of the failing circulation, by correction of the hypoxia, may be followed by increased diuresis

With the progressive hypoxia, a compensatory polycythemia is noted, "hypoxic erythrocytosis"[47] The hematocrit rises This polycythemia results in an increased blood volume and blood viscosity, manifested clinically by malaise, headache, dizziness, anorexia, plethora and distention of the neck veins In individual cases it may be

difficult to determine the exact point at which the compensatory polycythemia ceases to be beneficial and begins to increase the circulatory load When the vigorous measures noted above for relieving the hypoxia fail to bring about a reduction in the elevated hematocrit, prophylactic phlebotomies should be employed Since undesirable result may follow the sudden removal of more than 350 cc of venous blood, it is advisable to withdraw only 250 to 350 cc at one time, repeating the phlebotomies at intervals of a week or more, depending upon the clinical course The hematocrit may be used as a guide, and should be kept below 50 per cent Following venesection, the pulmonary arterial hypertension may fall to normal levels Recent reports have described effective pulmonary vasodilatation following the administration of tetra-ethyl ammonium chloride and Priscoline [65, 65]

B. *Aminophyllin*

Aminophyllin represents a safe, very reliable drug for the management of patients with cor pulmonale. Due to its direct action on the heart, Aminophyllin increases cardiac work and output[154] but its action is most remarkable in lowering peripheral resistance (more markedly in the pulmonary circulation than in the systemic), diminishing the right atrial pressure, and also dilating the bronchial tree [154, 160, 176] The impressive diminution of pulmonary arterial pressure (as much as 20 mm mercury fall in mean pressure) is achieved as a consequence of decreasing the resistance in the pulmonary circuit

The same category of patients will also benefit from the direct action of aminophyllin upon the kidney Renal plasma flow and glomerular filtration rate may be increased, due to the hyperemia resulting both from the larger cardiac output and from direct kidney stimulation [60] By inhibiting tubular resorption of the sodium, aminophyllin (alone or combined with mercurial diuretics) is a most valuable physiological tool in improving diuresis This procedure employing mercurial diuretics in combination with aminophyllin was used successfully by Vogl [165]

Aminophyllin can also serve as a means of evaluating the degree of reversibility of pulmonary hypertension. Lack of response to

aminophyllin indicates a poor prognosis The therapeutic effect from aminophyllin will be closely related to its level in blood plasma where it is only slightly bound to the serum protein. In general a level of at least 0 5 mg per 100 cc. of plasma is necessary.[154] Intravenous administration produces a high initial serum level, but there is a rapid drop, with complete disappearance from the serum at nine hours [166] Solutions of aminophyllin administered rectally can be given at six-, eight-, or twelve-hour intervals thus maintaining a continuous effective therapeutic level with minimum discomfort to the patient Bronchospastic crises may be prevented and better control of the dyspnea, orthopnea, and Cheyne-Stokes respirations can be observed. If the rectal route cannot be employed, fairly effective blood levels can be achieved by aminophyllin tablets, such as Cardalin which permits the administration of higher oral doses

C. Digitalis

The choice of digitalis preparations for controlling cardiac failure in these patients is not as important as a thorough knowledge of their variable speeds of action, their toxicities, and the full meaning of complete digitalization and daily-maintenance. Digitalization should be continued until signs of beginning compensation appear; then the patient should be placed on the daily maintenance dose If toxicity appears, digitalis should be omitted until these symptoms have subsided, before starting the maintenance dose The conventional average digitalization dose with Digitoxin is 1.2 mg., and the maintenance daily dose is 0 15 mg However, the range for complete digitalization may vary from less than 1.0 mg. up to 3.0 mg , and for daily maintenance, 0 1 mg up to 0 3 mg In general, one may give 0 6 mg Digitoxin by mouth and then 0 2 mg every six hours, until beginning compensation or toxicity is noted, before placing the patient on daily 0 2 mg maintenance It is our custom to digitalize with Digitoxin for rapid effect, but to maintain the patient with the whole-leaf digitalis preparation, with an average daily dose of 0 1 Gm daily.

Effect of Digitalis on Cardiac Output and Pulmonary Circulation

The exact role of digitalis in the management of chronic cor pulmonale is the subject of considerable controversy. The introduction

of the technique of cardiac catheterization and advances in the study of pulmonary function have yielded new data on its pharmacodynamics. The direct action of digitalis upon the fibers of the myocardium cannot be separated from its effect on venous pressure and on pulmonary circulation.

Digitalis will have little or no effect on cardiac output in the absence of heart failure[112, 176] and it should be employed when there is evidence of right ventricular failure. Digoxin or Digitoxin administered intravenously may be followed by striking improvement. Many investigators feel that Ouabain is superior to digitalis in initiating this improvement.[112, 184] The indication for the use of these preparations is the presence of failure, regardless of high or low cardiac output.

From the studies of Cournand, McMichael, Dexter and their associates[16, 61, 112] there emerges an over-all concept that cardiac output and failure do not always follow the same pattern in all patients. Furthermore, the level of the cardiac output should be looked upon as the individual response of each patient according to his own metabolic needs. No generalization of "high" or "low" cardiac-output type of failure can be adequate for each pathological entity causing cardiac failure. A patient may have different levels of cardiac output at different stages of cardiac decompensation.

A more comprehensive theory has been advanced by Ferrer *et al*[61] who studied a group of patients with cor pulmonale and right-sided heart failure before and after digitalization with a single intravenous dose of Digoxin. The first response was an increase in cardiac output and a reduction in the filling pressure of the right ventricle. Pulmonary artery pressure rose simultaneously, due to the increased blood flow into an already diminished pulmonary vascular bed. It is important to state, however, that this immediate response was of short duration. As time went on, clinical improvement of failure brought about a decrease in cardiac output, a reduction in the elevated pulmonary artery pressure, and improvement in the arterial oxygen saturation. In addition to the therapeutic effects of digitalis maintenance, the correction of polycythemia and hypoxia was of great help in reversing the pulmonary hypertension.

In the presence of left heart failure without primary pulmonary disease, acute digitalization by the intravenous route produces an

aminophyllin indicates a poor prognosis. The therapeutic effects from aminophyllin will be closely related to its level in blood plasma, where it is only slightly bound to the serum protein In general a level of at least 0 5 mg. per 100 cc. of plasma is necessary.[184] Intravenous administration produces a high initial serum level, but there is a rapid drop, with complete disappearance from the serum at nine hours [166] Solutions of aminophyllin administered rectally can be given at six-, eight-, or twelve-hour intervals thus maintaining a continuous effective therapeutic level with minimum discomfort to the patient Bronchospastic crises may be prevented and better control of the dyspnea, orthopnea, and Cheyne-Stokes respirations can be observed If the rectal route cannot be employed, fairly effective blood levels can be achieved by aminophyllin tablets, such as Cardalin, which permits the administration of higher oral doses

C Digitalis

The choice of digitalis preparations for controlling cardiac failure in these patients is not as important as a thorough knowledge of their variable speeds of action, their toxicities, and the full meaning of complete digitalization and daily-maintenance Digitalization should be continued until signs of beginning compensation appear; then the patient should be placed on the daily maintenance dose If toxicity appears, digitalis should be omitted until these symptoms have subsided, before starting the maintenance dose The conventional average digitalization dose with Digitoxin is 1 2 mg , and the maintenance daily dose is 0 15 mg However, the range for complete digitalization may vary from less than 1 0 mg up to 3 0 mg , and for daily maintenance, 0 1 mg up to 0 3 mg. In general, one may give 0 6 mg Digitoxin by mouth and then 0 2 mg every six hours, until beginning compensation or toxicity is noted, before placing the patient on daily 0 2 mg maintenance It is our custom to digitalize with Digitoxin for rapid effect, but to maintain the patient with the whole-leaf digitalis preparation, with an average daily dose of 0.1 Gm. daily.

Effect of Digitalis on Cardiac Output and Pulmonary Circulation

The exact role of digitalis in the management of *chronic cor pulmonale* is the subject of considerable controversy. The introduction

[o]f the technique of cardiac catheterization and advances in the study [o]f pulmonary function have yielded new data on its pharmacodynamics The direct action of digitalis upon the fibers of the myocardium cannot be separated from its effect on venous pressure and on pulmonary circulation

Digitalis will have little or no effect on cardiac output in the absence of heart failure[112, 176] and it should be employed when there is evidence of right ventricular failure Digoxin or Digitoxin administered intravenously may be followed by striking improvement Many investigators feel that Ouabain is superior to digitalis in initiating this improvement [112, 184] The indication for the use of these preparations is the presence of failure, regardless of high or low cardiac output

From the studies of Cournand, McMichael, Dexter and their associates[46, 61, 112] there emerges an over-all concept that cardiac output and failure do not always follow the same pattern in all patients Furthermore, the level of the cardiac output should be looked upon as the individual response of each patient according to his own metabolic needs No generalization of "high" or "low" cardiac-output type of failure can be adequate for each pathological entity causing cardiac failure A patient may have different levels of cardiac output at different stages of cardiac decompensation

A more comprehensive theory has been advanced by Ferrer *et al* [61] who studied a group of patients with cor pulmonale and right-sided heart failure before and after digitalization with a single intravenous dose of Digoxin The first response was an increase in cardiac output and a reduction in the filling pressure of the right ventricle Pulmonary artery pressure rose simultaneously, due to the increased blood flow into an already diminished pulmonary vascular bed It is important to state, however, that this immediate response was of short duration As time went on, clinical improvement of failure brought about a decrease in cardiac output, a reduction in the elevated pulmonary artery pressure, and improvement in the arterial oxygen saturation In addition to the therapeutic effects of digitalis maintenance, the correction of polycythemia and hypoxia was of grea[t] help in reversing the pulmonary hypertension

In the presence of left heart failure without primary pulmonar[y] disease, acute digitalization by the intravenous route produces a

immediate fall in pulmonary artery pressure, since the increased cardiac output finds its way through a readily distensible pulmonary vascular bed where no abnormal resistance is encountered.

The mechanisms discussed above have been interpreted by Ferrer *et al* in a schematic figure (Fig. 19).[61, 62] It is likely that increases in

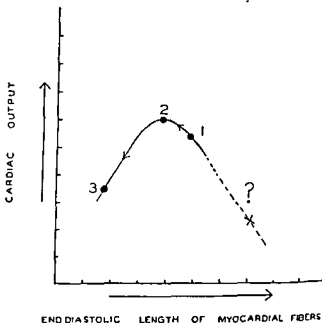


FIG 19 —Schematic curve relating changes in cardiac output and changes in myocardial fiber length at the end of diastole in chronic cor pulmonale (Reprinted through the courtesy of Dr. I M Ferrer)

blood volume and cardiac output occur in patients with cor pulmonale and emphysema prior to the onset of right heart failure (from an average normal position #3 to position #2) When failure occurs, the cardiac output declines from the previous high level to a lower one which is, nevertheless, still above a normal output (from position #2 to position #1) If, at that time, the patient receives Digoxin, the cardiac output at first rises, in order to empty the failing ventricle of its excessive residual volume (from position #1 back to position #2) Subsequently, with continuation of Digoxin and the judicious

use of phlebotomy and bronchodilators, the cardiac output will tend to return toward normal (position #3) This is effected by the more adequate emptying of the right ventricle and the shortening of the initial diastolic length of the myocardial fibers. The pulmonary artery pressure diminishes as a result of the reduction in blood flow and the correction of hypoxia and polycythemia

These studies should dispel the fear of some clinicians that digitalization may be harmful in the stage of the circulation just prior to frank failure of the right heart It is possible that the "ill effects" or "failure to improve," often reported after the use of digitalis in such cases, may have resulted from the simultaneous injudicious administration of high concentrations of oxygen On the other hand, failure in improvement may have been due to the presence of primary pulmonary arteriosclerosis In addition to digitalis, salt restriction, ammonium chloride and the mercurial diuretics should be employed in the treatment of cardiac failure The use of cation exchange resins with supplemental potassium therapy may be helpful when the above procedures fail

Finally, for the patient with intractable failure, there is the intriguing possibility of employing radioactive iodine (I^{131}) therapy Production of hypothyroidism by this technique, in previously euthyroid individuals, may permit the patient's heart to function more adequately since the oxygen requirements will then be lower than in normals Not only is the metabolic oxygen need of the body as a whole lessened but that of the myocardium decreases in the same fashion.

D *Mercurial Diuretics*

The control of hypervolemia by the employment of mercurial diuretics may be of great value in the management of the patient with cor pulmonale, even when evidence of frank failure is lacking. The effect of diuresis induced in this manner is to diminish the total amount of extracellular body fluid, this action is supplemental to diminution of the total red blood cell mass by phlebotomy Pulmonary vascular engorgement and minimal degrees of pulmonary edema can be relieved

The time-dose relationships of mercurial diuretics have been carefully studied [71] Frequent small doses, maintaining a continual state

of diuresis, are preferable to larger doses administered at longer intervals. The profuse diuresis which occurs in the latter situation often leads to such great and sudden loss of sodium ions in the urine as to produce symptoms suggesting Addison's disease, such as anorexia, weakness, fatigue and leg cramps. The dosage of these agents is best controlled through daily observation of the weight of the patient on arising. A dosage and interval between doses should be employed which will maintain the patient at or near his "dry weight" with minimum of fluctuation in weight. Moderate weight loss of from two to four pounds following the mercurial injection is more desirable than a pronounced weight loss.

Patients with chronic pulmonary disease and cor pulmonale may have a respiratory acidosis. Increased renal excretion of chloride ions compensates for the respiratory acidosis in this situation, these patients usually have hypochloremia. Chloride diuresis, as may occur with mercurials, thus has the added danger of creating a profound hypochloremia. This may be avoided by the simultaneous daily administration of 2 to 6 Gm. ammonium chloride. If one prefers to employ the mercurial diuretics spaced farther apart and in larger doses, ammonium chloride should be given in divided daily doses of 4 to 6 Gm. for two days prior and on the actual day of administration of the mercurial diuretic. This will serve to enhance its diuretic effects.

Although it is seldom desirable, the ammonium chloride might be deliberately withheld in patients with very high arterial pCO_2 and uncompensated respiratory acidosis, while mercurial diuretics are administered, deliberately provoking further hypochloremia as a compensatory metabolic alkalosis. The quantitative nature of this acid-base equilibrium and the ease with which it becomes disturbed require frequent determinations of the plasma levels of bicarbonate, chloride and the pH.

Extreme hyponatremia due to sodium diuresis should be avoided. Moderate restriction to 3 to 5 Gm. of salt daily should be attempted before resorting to a more intensive restriction of as little as 200 mg of sodium each day. Careful attention should be given to the palatability of the salt restriction diet and the use of salt-poor dietary supplements.

E Sedation

It is best to avoid heavy sedation, as the incidence of obstructive asphyxia and pulmonary edema is higher in the deeply sedated patient. The barbiturates and morphine depress the respiratory center until it is less sensitive than normally to stimulation Phenobarbital in oral doses of 30 to 60 mg may produce adequate relaxation in the mildly dyspneic patient Sodium Pentothal should not be employed, for it may cause bronchoconstriction The combination of chloral hydrate and sodium bromide may be quite helpful, these can be given rectally in doses of from 1 to 3 Gms each and may be repeated at twelve-hour intervals for several days without fear of serious respiratory depression Doses of from 20 to 30 cc of paraldehyde, combined with an equal amount of olive oil or prepared as a cornstarch emulsion, may be administered high-rectally at twelve-hour intervals When sedation to the point of actual light anesthesia is required, ether is the agent of choice It may be administered in doses of from 60 to 90 cc dissolved in an equal amount of sweet oil placed high in the rectum. This dose may be repeated at eight-hour intervals for one or two days

1 Morphine

Morphine does not produce a significant change in the heart or the circulation Respiratory and metabolic rates tend to drop progressively, and with larger doses the cardiac output and cardiac work will decrease slightly[154] Occasionally, following the initial use of morphine sulfate (8 to 10 mg subcutaneously), one sees very striking relief of dyspnea, in the chronically ill patient with bronchitis and emphysema who is suffering from a paroxysm of bronchoconstriction

However, morphine should not be employed in patients with bronchial asthma or emphysema, because with repeated doses serious sequelae may follow Such therapy has been decried for many reasons[125, 161] On the whole, morphine tends to depress the respiratory center It decreases the respiratory rate, diminishes the tidal volume, and decreases the minute volume of respiration, thus accentuating the degree of hypoxia It also depresses the cough reflex and prevents

effective expectoration, thereby increasing the tendency toward segmental atelectasis Frequently morphine appears to produce additional nausea and vomiting, and there is always the possibility of hypersensitivity and even addiction. Finally, death following morphine therapy has been reported frequently, in status asthmaticus and chronic cor pulmonale with kyphoscoliosis and in most instances the deaths could be attributed to its use We have found in Nalline, N-allyl-normorphine hydrochloride, an effective morphine antagonist and direct stimulant of the respiratory center.[84] This drug should be employed in such instances.

2 Demerol Hydrochloride (Meperidine)

Demerol has a wider range of safety than morphine, and is a more efficacious drug in the treatment of the very sick emphysematous patient, since it is extremely helpful in relieving an intractable or utterly useless cough It may be given in doses of from 50 to 100 mg intramuscularly or 100 to 150 mg. orally at eight- or twelve-hour intervals for three to five days The use of smaller doses at the outset, however, may minimize any side reactions Some bronchodilatation, mild sedation and atropine-like effects may occasionally be observed, and a few patients will complain of nausea or dizziness The majority of patients, however, enjoy a pleasant stage of general relaxation following its use Tachyphylaxis is occasionally noted but full response usually returns after a rest period Addiction to meperidine, although less frequent than to morphine, does occur and may be of a severe type

Despite the comparative safety of Demerol, it is advisable that neither Demerol nor morphine be employed in the patient with chronic cor pulmonale associated with kyphoscoliosis or chronic pulmonary emphysema The reduction in pulmonary ventilation which follows in such instances causes further hypoxia and cyanosis The subsequent danger of the carbon dioxide intoxication syndrome and respiratory acidosis when high oxygen concentrations are added has been previously described. (See Chapter V.)

CHAPTER VII
Symptomatic Treatment

Skillful management of the patient suffering from chronic pulmonary emphysema depends on a thorough knowledge of the pathologic physiology of the disease and precise interpretation of the clinical signs and symptoms perceived at the bedside The program of therapy should be designed with a view toward removing the cause of the disease, preventing exacerbations, and slowing the progress of destruction in the lung parenchyma, but above all, toward giving the patient all the comfort possible Countless patients are condemned to years of discomfort by the pessimistic attitude prevailing among many physicians toward the value of symptomatic therapy that could afford gratifying, if only partial, relief

Evaluation of the comparative importance of bronchial and parenchymal factors in the individual patient will permit more rational therapy In every case, the various occupational, infectious, or allergic precipitating factors should be analyzed with great care

The more extensive the underlying bronchitis, the greater th likelihood of diffuse bronchoconstriction and tendency toward th development of bronchospastic paroxysms When parenchymal dan age is more prominent, loss in vascularity, weakening of alveol walls, replacement of elastic tissue by fibrous tissue, and finally t

failure of adequate expiratory force, indirectly causes further bronchoconstriction which leads to the trapping of air with each inspiration and increase in pulmonary overdistention.

With these basic ideas in mind, a program of symptomatic care for the patient with chronic pulmonary emphysema will be discussed under the following headings:

I. General Considerations

A. Occupation

The hazards of the patient's occupation should be scrutinized and precautions taken to reduce them to a minimum Exposure to asbestos and silicon and the hazards of hard and soft coal mining are not the only direct insults to the pulmonary parenchyma. Safeguards are necessary against the inhalation of nonspecific dusts, fumes, and vapors which are also irritants that may be responsible for a continued bronchitis with destructive sequellae Improvement in working conditions has resulted from such protective measures as oiling to keep dusts from flying about, watering the ore loads in mines and the brushes of cotton workers, and using face masks, improved ventilators, suckers, blowers, and air conditioners, for filtering as well as for cooling and dehumidifying

B. Allergies

Every measure that offers the possibility of preventing or minimizing attacks of bronchitis should be utilized If specific allergens cannot be removed from the environment, the patient's tolerance to them should be improved Specific measures of treatment such as hyposensitization, although too often disappointing, are still worth a trial in patients with chronic pulmonary emphysema secondary to bronchial asthma, if the underlying allergy can be determined Our experience with the use of dust and bacterial vaccines, both stock and autogenous, has been disappointing. Control of the allergic aspects of the problems of chronic pulmonary emphysema by means of antihistaminic agents, ephedrine, aminophyllin, and corticotropin will be discussed individually.

C. Infections

Oral sepsis and infected sinuses, tonsils, and adenoids should be treated specifically—surgically if indicated. Patients should be warned against hazards of upper respiratory infections and overexertion. Either of these factors may disturb the complicated homeostatic mechanism and suddenly produce more severe pulmonary insufficiency. Recovery from these episodes is slow, but fortunately most of these physiologic changes are reversible with vigorous therapy.

D. Surgical

On occasion the physician is confronted with the problem of whether or not to recommend excisional therapy (lobectomy, pneumonectomy, or segmental pulmonary resection) for removing giant air cysts, infected air cysts, areas of atelectasis and bronchiectasis, areas of tuberculous cavitation, or other diseased conditions of the lung. In general, if mechanical bronchial compression or a chronic nidus of infection is present, surgery should be attempted. Although many of these patients are benefited by surgery, it should be kept in mind that removal of bronchiectatic segments may not cure the underlying bronchitis. The presence of residual bronchiectasis, either overlooked by failure to map out the lungs completely before surgery or because the case was considered unsuitable for further resection, may prevent complete relief of the patient's symptoms.

E. Climate

The progress of the disease may be influenced by many physical factors, such as the range of changes in temperature and barometric pressure, the humidity, wind variability, and proximity to the seashore, the amount of sunshine, the altitude, and other factors. If a choice of residence is possible, the patient should avoid localities and houses without excavated basements. Climatic changes at will being within the reach of relatively few, the physician should hesitate to urge such a program without carefully considering the many factors involved. Without actual trial residence for at least one year of consecutive seasons, it may be difficult to determine just what factor

does produce the improvement when the patient changes climate If a permanent change cannot be made, winter residence in a temperate climate may be feasible and helpful. Chasing the will-of-the-wisp of cure by climatic alteration may be financially ruinous, and should be advised with caution.

Patients with emphysema and coexisting heart disease should stay away from altitudes above 4000 feet Those with troublesome bronchitis and considerable sputum may prefer the dry, warm, and generally calm, climate of southern California or southern Arizona (Tucson or Phoenix) A dry climate may, on the other hand, be responsible for retention of mucus or obstructive phenomena. Those with scant and viscid sputum may fare better in the warm moist climate of Georgia, Florida, or along the Gulf Coast These regions are believed to influence infectious respiratory processes favorably.

Damp humid weather and especially fog are generally not well tolerated Atmospheres containing soot, fumes, and other chemical or mechanical irritants may also be harmful and should be avoided If pollen allergy is of major importance, careful determination of the tree, grass, and ragweed pollen indices of the selected site should precede contemplated residence.[119]

F. *Personal*

Before discussing symptomatic drug therapy, it should be stressed that the total needs of the patient as an individual must be integrated with his therapy Specific emotional factors, as well as fatigue or infection, can precipitate or modify a bronchospastic crisis After all, the patient with chronic pulmonary emphysema is not a person set apart, he is still subject to other ailments, and his physician should not fail to heed his varied complaints.

A distended stomach may provoke bronchial irritation; the patient should be warned that overindulgence in food or drink is therefore risky. Those patients that have gained too much weight should be placed on a weight reduction regimen with supplemental anorexigenic substances as needed The majority are unfortunately *too thin* and need to be encouraged to take appetizing foods and diet supplements.

The question of smoking may assume major proportions[120] It is

our feeling that tobacco should be given up Improved appetite and weight gain may follow. The cough usually becomes less troublesome and it may be observed that the irritated mucosa becomes less edematous and reddened To be sure, the inhalation of tobacco smoke affords a method of provoking the expulsion of retained secretions, but it does this at the hazard of setting up a state of chronic bronchial irritation

II. Bronchial Evacuation

The bronchitic cough is one of the most troublesome manifestations of chronic pulmonary emphysema and may actually serve as the trigger mechanism for more extensive bronchiolar spasm and alveolar disintegration Many expectorants and expectorant mixtures have been employed to combat it.

Evacuation of the bronchi ("bronchial catharsis") may be accomplished by physiologic mechanisms or by therapeutic mechanisms[139] The physiologic mechanisms are (a) the cough reflex, which functions in the upper airways, (b) ciliary action which functions down to the fine bronchioles, and (c) peristaltoid wave motions, which function to evacuate the entire respiratory tract.[139] These physiologic activities may overlap Every attempt should be made to keep or restore these mechanisms in order to prevent tussive insufficiency and the trigger mechanism responsible for further damage.

The therapeutic mechanisms for bronchial evacuation consist mainly in the use of A Expectorants, B. Bronchodilator Drugs, C Postural Drainage, and D Bronchoscopy and Bronchoscopic Lavage

A Expectorants

The expectorant drugs may prove quite helpful when properly used. An effective productive cough should not be oversedated, or the mucus in the bronchioles may become tenacious and inspissated, largely from dehydration and long retention If the mucus is permitted to become impacted, the cough may become ineffective and a state of "tussive insufficiency" will develop.

The antihistaminic expectorant preparations such as Benylin Expectorant or Pyribenzamine Expectorant, are preferred by some patients, particularly those with associated vasomotor rhinitis The

Benadryl in the former may serve as a mild sedative. The ephedrine in the Pyribenzamine combination may be slightly stimulating. These preparations, however, tend to dry up secretions in some patients, and may actually be responsible for their dry, persisting, cough Hydryllin compound has the advantage of containing aminophyllin in addition to diphenhydramine. We have recently employed Toryn, 10 mg every six hours, in syrup or tablet form. It is an effective antitussive agent whose properties are primarily anticholinergic, but it is essentially free of undesirable atropinelike side effects such as mydriasis, dryness of mouth etc Toryn has been well tolerated and appears to control hacking "bronchitic" cough

Iodides may be prescribed with these expectorants to promote more adequate "bronchial catharsis" in the more severe forms of bronchitis There is ample evidence that they stimulate bronchial secretion and are excreted into these secretions within fifteen to twenty-five minutes after their administration, whether oral or intravenous[155, 159] Their action also results in dilution and liquefaction of the retained secretions.

Iodides are generally more efficacious when the patient is well hydrated. A disagreeable metallic, bitter taste is commonly experienced but is generally not too objectionable. The usual precautions in the use of iodides must be observed, namely, close watch must be kept for evidence of a variety of rashes and swellings, conjunctivitis, coryza, bronchorrhea, thyroiditis, and adenopathy. Iodides should not be used if there is evidence of thyroid adenoma, pulmonary edema, or pulmonary tuberculosis

A preliminary test for idiosyncrasy (0 1 cc. of a saturated solution of potassium iodide orally) should be made on all asthmatic patients who are to receive iodides in any form, including radio-opaque materials for endoscopic therapy or bronchographic visualization Administration should proceed cautiously. The initial dose should be 0 2 cc. of the saturated solution of potassium iodide after each meal and at bedtime. This may be increased by 0 1 cc. per dose each day until a maximum dose of 1 3 cc. is reached. The dose should then be abruptly reduced to 0 2 cc and the same gradual increase of dosage repeated; this may prevent the development of intolerance. For patients in whom gastric irritation develops from a saturated solution of potassium iodide, enteric-coated tablets, Enkide, are available in 0 5 Gm. and 1 0 Gm sizes

Persistent cough not allayed by the combination of iodides with Hydryllin or Toryn may be favorably influenced by dihydrocodeinone, a codeine derivative that gently suppresses the cough reflex without producing the constipation noted from codeine. Nausea may occasionally be troublesome with the use of this medication

B Bronchodilator Drugs

Ephedrine sulphate is a favorite remedy for the treatment of bronchitis and bronchoconstriction The British recommend large single doses that exceed 30 mg [84] In our experience these doses prove too stimulating and are often associated with side effects such as insomnia and palpitation Ephedrine should be used with caution in the presence of prostatism, as delayed bladder emptying and obstruction may appear This drug is poorly tolerated by many patients that have associated hypertension and cardiac irregularities Refractoriness to ephedrine may appear in patients who show initial response Small doses, up to 25 mg , may be found useful in mild cases, particularly *when combined with effective doses of aminophyllin* The pharmacologic effects of ephedrine, although to a lesser degree than those of epinephrine, produce tachycardia, elevation of systemic blood pressure, increased respiratory volume, increased cardiac output, and increased cardiac work with an associated drop in peripheral resistance [154] Many observers have found Orthoxine as effective as ephedrine but freer of side reactions

Intramuscular epinephrine, 1.1000 solution, although capable of relieving bronchospasm, should be employed sparingly because of its effects on the pulmonary vascular bed Zimmerman[176] has shown that intramuscular epinephrine produces pulmonary arteriolar constriction and a further (temporary) rise in pulmonary arterial hypertension This may result from the effect of epinephrine in increasing the cardiac output and blood flow into the pulmonary vascular tree The already reduced pulmonary vasculature cannot compensate by sufficient vasodilation and a rise in pulmonary arterial pressure follows Fortunately, these effects of epinephrine rapidly disappear and the pulmonary arterial pressure returns to its previous level

Aminophyllin (theophyllin ethylenediamine) produces varied responses Some patients become more alert, others become drowsy, many become nauseated and even vomit, and still others complain of

palpitation and sweating There are many oral medications combining aminophyllin (or similar derivatives) with ephedrine (or similar derivatives) and some form of sedative available for the relief or prevention of mild but chronic bronchoconstriction. The disadvantage in most of these preparations, however, lies in the side reactions that appear when using the high dosage of aminophyllin necessary to achieve therapeutic results

The addition of antinausea factors (local and central) to aminophyllin has recently made possible oral administration of larger effective doses of aminophyllin, with or without ephedrine or a barbiturate. Such a combination is represented in Dainite and Cardalin [146] The dosage of Dainite in mild but chronic bronchoconstriction is one Day tablet before each meal and one Nite tablet before retiring. A slightly lower or upward revision of dosage may be found necessary.

Aminophyllin blood levels of about 0.5 mg. per 100 cc may be necessary when bronchospasm is persistent, particularly if it is associated with chronic bronchial asthma. These levels are difficult to achieve through oral administration of the drug, because of the side reactions, but can be obtained through the use of aminophyllin solutions given rectally or intravenously. The rectal dose is from 0 3 to 0 5 Gm of a 2 per cent solution, given just before the patient goes to sleep at night and as soon as he wakes up in the morning This schedule may be continued indefinitely, when necessary, or one or both doses may be omitted after sufficient improvement occurs. In severe cases, the Dainite tablets may be used to supplement the rectal aminophyllin, or to replace it when continued improvement has been noted. We have found liquid and dust aerosols of aminophyllin of no significant value The use and physiologic effectiveness of aminophyllin have been discussed more fully in Chapter VI.

C. *Postural Drainage*

While of little benefit to those with useless cough, postural drainage may be of considerable value to the patient with accumulated secretions that are easily raised The procedure is generally most efficacious in the management of associated bronchiectasis.

Patients who are physically able to do so, are urged to cough as

much as possible in the position that will best utilize the force of gravity as an aid to drainage. The proper position can facilitate drainage of any particular involved part of the bronchial tree. Most patients soon learn the best position for raising the maximal amount of sputum. Some are able to thoroughly empty their lungs of accumulated secretions in the morning and remain free of cough all day.

The most dependent segments of the lung can be evacuated if the patient kneels in bed, facing out, his knees at the edge, places both elbows before him on a stool low enough to allow the thorax to assume as nearly vertical a position as possible, and coughs and expectorates for several minutes while in this position. This exercise should be performed before meals and at bedtime. Postural drainage is more effective when carried out after bronchodilator therapy. Penicillin aerosol will be more effective after postural drainage.

D. Bronchoscopy and Bronchoscopic Lavage

Bronchoscopy is a very valuable diagnostic and therapeutic procedure. It is indicated whenever a harsh useless cough with dammed-up secretions is present and whenever bronchospasm persists despite adequate therapy as outlined. It may be of extreme value in the febrile state, in the prevention or treatment of segmental atelectasis, and in obstructive emphysema. The early stage of obstructive emphysema must be recognized promptly, if complete bronchial obstruction is to be prevented. Through bronchoscopy, tenacious and thick gelatinous sputum may be removed, large amounts of thinner secretions aspirated, and bronchial drainage facilitated.

To be complete, bronchoscopic examination should conclude with aspiration of the retained secretions, and the secretions and material carefully preserved, cultured, and studied by special staining techniques for organisms and cells. Intrabronchial instillation of suspensions of penicillin or streptomycin, or both, in a detergent solution should follow aspiration.

For lavage, saline or Zephiran solutions 1:5000 are preferred by many. In an interesting technique for pulmonary lavage at the time of bronchoscopy, based on the principle that lavage is most effective in the dependent portions, Harken tries to make the lower lobes and anterior portions of both lungs dependent by rotating the patient in

various positions.[80] This rotational positioning also permits more thorough bronchoscopic evaluation.

Because of the danger of serious reactions to the use of Pontocaine or cocaine sprays and instillations for local anasthesia in the allergic patient, we have generally advised deep surgical anesthesia with ether.[139] More recently, the empiric use of corticotropin prior to bronchoscopic as well as bronchographic procedures has appeared advisable for preventing Pontocaine, cocaine, or Lipiodol reactions in patients with a history of previous sensitization to these substances or with a known history of associated chronic bronchial asthma.[114]

When iodized oil visualization in bronchoscopy is necessary in the allergic patient, the following regimen may be employed. Corticotropin, 20 mg. every 5 hours for 3 doses, is given intramuscularly on the day before the procedure. Pentobarbital sodium, 0.1 Gm., is given the night before and again one hour before the patient goes to the x-ray department for the Lipiodol instillation. At this time, a continuous intravenous infusion of one liter of 5 per cent glucose in distilled water with 20 mg. corticotropin and 0.5 Gm. aminophyllin is started, the flow being at the rate of 60 drops per minute. Very anxious or dyspneic patients receive from 75 to 100 mg. of meperidine hydrochloride subcutaneously with the pentobarbital sodium 0.1 Gm. just before the intravenous infusion is started. Adequate topical anesthesia with 1 per cent Pontocaine is employed. Immediately after Lipiodol instillation, the bronchograms are taken and the patient is removed to the bronchoscopic room. The Lipiodol and secretions are aspirated with the positional technique, after which bronchoscopic visualization and lavage is carried out.[80]

III. Drugs and Procedures to be Avoided or Employed with Caution

A large percentage of patients with chronic paranasal sinus disease, nasal polypi, bronchial asthma, and chronic pulmonary emphysema are unusually sensitive to aspirin. Swelling of the mucous membranes of the mouth, larynx, and bronchi may follow instantaneously after the empiric use of aspirin or the use of penicillin dust or aerosols to

combat bronchiolar infection. The indiscriminate use of cocaine nasal packs should be avoided in this group of patients.

We have stressed the high incidence of drug idiosyncrasy and allergy in these patients, particularly with topical administration It is also stressed that the use of respiratory-depressing drugs and the sudden administration of high concentrations of oxygen, alone and more particularly in combination, should be avoided

CHAPTER VIII
Therapeutic Aerosols and the Management of Infection

I. Sympathetic Amine Aerosols

A. Indications

Bronchodilator aerosols are of great value in the treatment of chronic bronchial asthma, but unfortunately they have not been employed as wisely as is desirable in the management of emphysematous patients Whether or not chronic pulmonary emphysema is secondary to bronchial asthma, once it has become established this disease frequently requires the use of bronchodilator aerosols

As previously described (Chapter II), bronchoconstriction plays either an intermittent or a continuous role in the evolution of chronic pulmonary emphysema Consequently a quick method for relieving bronchoconstriction may at times be necessary. Relief of (acute) hypoxia in these patients by the use of oxygen alone cannot be accomplished adequately in a short period. Along with the oxygen therapy an effective bronchodilator should be employed, together with appropriate measures to secure a clear airway. This procedure may be compared with the synergistic utilization of digitalis and mercurials in the management of heart failure.

In addition, bronchodilator aerosols are quite useful for determining rapidly the degree of reversibility of pulmonary insufficiency, and possibly the degree of reversibility of pulmonary arterial hypertension (Chapter VI). This may be of some importance from a prognostic point of view.

Finally, bronchodilator aerosols should be administered routinely when antibiotic aerosol therapy is used in patients with chronic pulmonary emphysema This combination allows maximum penetration and deposition of the antibiotic in areas of lung otherwise restricted because of poor ventilation Small infectious nidi—a very common occurrence in chronic pulmonary emphysema—are best treated in this manner.

B. Technique

Aerosols of the sympathomimetic drugs, Vaponefrin (2 25 per cent racemic epinephrine hydrochloride) and Isuprel (1-3′4′-dihydroxyphenyl-2-isopropylaminoethanol hydrochloride, 1:200), are of great value for the relaxation of bronchospasm In common with the majority of investigators, we have found the Vaponefrin nebulizer most satisfactory for the production of therapeutic aerosols It produces a fine, voluminous mist or smoke screen, in which the majority of the particle radii average about 1 micron and are thus able to penetrate the smaller bronchioles and alveoli As little as 0 05 to 0 10 cc of one of these solutions (neubulized by three to six compressions of a hand bulb) may abort or relieve a mild broncho-spastic episode

Many patients are advised to take these inhalations before meals and at bedtime. Patients who are embarking on a program of breathing re-education or postural drainage are advised to take this treatment before starting their programs More severe bronchospasm may require 0 5 to 1 0 cc of the bronchodilator solution, nebulized by continuous flows of oxygen or helium-oxygen, or by air pump This treatment generally requires from five to fifteen minutes at five-liters-per-minute flow A Y tube or simple button-like opening can be inserted into the oxygen or air-feed line Thumb closure during inspiration permits a continuous flow, whereas removal of the thumb during expiration interrupts the aerosol production

Substituting helium and oxygen mixtures for oxygen is of further value if there is evidence of bronchial obstruction The helium-oxygen mixture allows the nebulized solutions (Vaponefrin, Isuprel, Neo-Synephrine, penicillin, Terramycin, or streptomycin) to pass through the contracted bronchi more freely, and permits these preparations to act more effectively on the mucosa and submucosa

Aerosols may be introduced along with intermittent positive-pressure breathing with the Bennett, Emerson, or the M S A. pulmonary

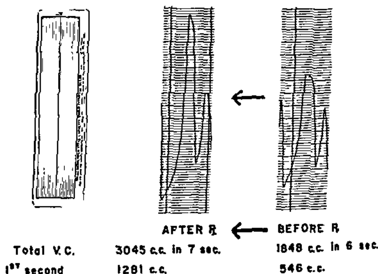


Fig 20 —Vital capacity–time relationships

ventilator valves, thus combining the physiologic advantages of bronchodilation with those of improvement in alveolar functioning

Following bronchodilator aerosol therapy, improvement in the time-vital capacity relationships is uniformly observed [115] In Fig. 20, there is an illustration of the improvement in these relationships after inhalation of Vaponefrin aerosol (six inhalations) in a patient with chronic pulmonary emphysema.

It will be noted that the greatest improvement occurs during the first second. In determining time-vital capacity relationships, we employ a simple ruler transparency, shown on the left in Fig 20

This transparency is placed over the kymograph tracing, and the volume of air exhaled during any time-interval of the vital capacity curve is computed directly (see "Methodology," Fig 30)

Bronchodilator aerosols are often helpful in converting a useless cough into a productive one Where refractoriness or toxicity has been noted following the use of these bronchodilators, tolerance may be restored with Neo-Synephrine aerosols (0 25 to 1 per cent) Neo-Synephrine aerosols also produce effective broncho-vasoconstriction, which reduces mucosal congestion without the secondary vasodilatation which may occur when topical epinephrine preparations alone are used Neo-Synephrine is useful in diminishing the vascular engorgement usually present in the pulmonary vascular tree In patients with mild bronchoconstriction, these agents may be combined

II. *The Management of Infection*

Whether or not infection is the primary cause, it plays a definite role in the pathogenesis of chronic pulmonary emphysema Infection may act in any of the following ways

(1) True immunological sensitization (bacterial allergy), precipitated by an upper respiratory tract infection, may initiate the bronchial asthma responsible for the chronic pulmonary emphysema

(2) Secondary respiratory infections may begin in poorly aerated lung segments A bronchitis may be initiated, and paroxysms of cough and wheezing may persist Recurrent winter upper respiratory infections may bring on the so-called "old man's winter cough" An atelectatic or bronchiectatic area may serve as a nidus for recurring pneumonitis

(3) Adenoid hypertrophy and infection, nasal polyps and paranasal sinus disease, once established, are responsible for the chronicity of the sinobronchitic disease

A Aim of Antibiotic Therapy

The aim of therapy which employs antibacterial agents in the management of patients with bronchopulmonary infection is to produce as high a local concentration as possible of the antibacterial agent in the sputum, tracheobronchial tree, and the pulmonary tissues The use of antibiotic aerosols for this purpose may be of

especial value Every attempt should be made to identify the organisms from the nose, throat, and sputum before, during and after treatment The emergence of new bacterial flora should be looked for [167] Changes in the bacterial population, and particularly reinfections due to these bacteria, fungi or molds, occur following all types of antibiotic therapy, and may be responsible for serious secondary infections (1 to 2 per cent incidence). These secondary organisms are generally insensitive to the primary antibiotic employed Whenever feasible, sensitivity tests of the identified organisms to the antibiotic should be made, particularly if therapy is prolonged

B. Methods of Administration and Choice of Antibiotic Aerosols

The choice of the antibiotic drug depends on the predominating organisms, their sensitivity, and the patient's tolerance to the drug itself [15, 137] Penicillin is generally employed for gram-positive organisms, Streptomycin is added or used alone, if gram-negative bacteria are also present or emerge. Recently we have been employing Terramycin aerosol when broad spectrum antibiotic therapy is indicated

The antibiotic aerosols may be combined with equal amounts (*e g*, 1 cc each) of the bronchodilator preparations or detergent antiseptics, such as aqueous Zephiran 1:1000. A few drops of Duponol-C, 5 per cent, or Alevaire may be employed instead of Zephiran to lower the surface tension when greater penetration is desirable Crystalline penicillin in doses of 50,000 to 100,000 units, alone or with 0 1 Gm streptomycin, is dissolved in the desired bronchodilator solution or combined solutions. With the techniques described above, treatments may be given at four-to-six-hour intervals A course of therapy may range from one to six weeks, depending on the severity of the underlying infection and the general progress of the patient We have observed that most of our patients have been able to raise sputum more easily while receiving these aerosols

The hazard of local or generalized allergic reaction to penicillin aerosol in patients with underlying bronchial asthma must never be overlooked. On occasion, we have noted the onset of mild bronchial asthma in patients receiving penicillin aerosol therapy for the man-

agement of chronic bronchitis, emphysema, or bronchiectasis. However, these attacks subsided promptly, when Vaponefrin inhalations were given after the penicillin aerosols had been discontinued. Oral antihistaminic preparations may prevent or minimize these reactions, permitting the continuation of the therapy.

C. Supplemental Antibiotic Agents

If there is clinical evidence of respiratory tract infection with roentgenographic confirmation of pneumonitis, atelectasis, or bronchiectasis, supplemental parenteral penicillin or streptomycin should be employed, or one of the broad spectrum antibiotics, Aureomycin or Terramycin. Combined aerosol and parenteral therapy will ensure also against local or systemic spread of the infection. It should be noted that adequate parenteral therapy affords another route to reach poorly ventilated areas. Sputum cultures should be observed closely, the occurrence of Monilia and gram-negative bacteria may be noted appearing after the employment of penicillin. The "emergence" of other than the original pathogenic organisms (e.g., *Staphylococcus aureus, coagulase positive*, or *Bacillus proteus*) may be noted, particularly when the bacteriostatic broad spectrum antibiotics are employed.

In general, penicillin administered parenterally in conventional dosage, despite adequate systemic blood levels, has failed to get into the sputum in high enough levels, in patients with chronic suppurative disease. This appears to be particularly true of patients with chronic pulmonary emphysema, because of the restricted pulmonary vascular bed, alveolar disintegration and peribronchial fibrosis. We have found that Neo-Penil, a hydriodide ester of penicillin, formed from penicillin and diethylaminoethyl alcohol by the removal of water, given intramuscularly in doses of 500,000 units every eight hours, produces essentially low systemic blood levels with high concentrations in the sputum.[148]

Other investigators have been able to demonstrate lung tissue concentrations several times greater than those achieved with comparable doses of crystalline or procaine penicillin and there is evidence that the lung tissues act as a depot for the unhydrolyz[ed] accumulation of Neo-Penil. Following hydrolysis by body fluids, t

Neo-Penil is apparently gradually released to the blood stream as free active penicillin The present evidence indicates that this is an effective form of penicillin in patients with chronic pulmonary emphysema and bronchopulmonary infection.[19, 37, 78]

We have assayed the blood and sputum levels in 6 patients following the administration of single intramuscular doses of 300,000, 500,000,

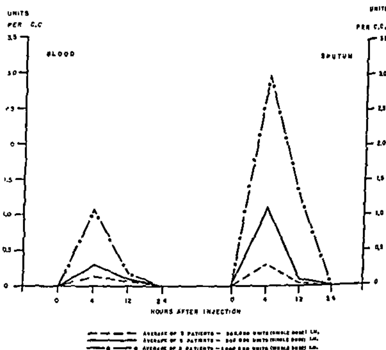


FIG 21 —Neo-penil concentrations in blood and sputum

and 1,000,000 units of Neo-Penil.[67] Four-hour peak levels were determined in the blood and sputum The blood peak levels ranged from 0.1 to 1 1 units per cc. The sputum peak levels in the same patients ranged from 0 35 to 3 0 units of Penicillin per cc. (Fig. 21).

D. *Preventive Use of Antibiotic Agents*

The exact value of the prophylactic use of antibacterial agents is most difficult to determine in the prevention of disabling upper

respiratory tract infections in patients with chronic pulmonary emphysema. There are many pathogenic and nonpathogenic bacteria, fungi, and viruses which initiate such infections It is doubtful whether immunological resistance to these organisms can be obtained from the use of mixed stock or autogenous vaccines It does appear advisable in selected patients, however, to employ prophylactic oral sulfonamide, penicillin, or broad spectrum antibiotic agents (Terramycin or Aureomycin) Sensitivity reactions, resistance, and superimposed infections may occur, but the need may well justify the risk, inasmuch as their incidence is low

Prophylactic therapy is of particular value in (1), debilitated patients with intractable bronchitis, (2), those with chronic cor pulmonale, and (3), patients subject to recurrent respiratory tract infections during the winter months In general, we have employed orally one of the following antibiotics sulfadiazine 0 5 Gm every eight hours, penicillin 200,000 units every twelve hours, Aureomycin or Terramycin 100 mg every eight hours These doses may require slight upward revision, this therapy should be continued for approximately five months during New England winters

The periodic examination of the patient should include blood and urine studies for possible manifestations of toxicity or idiosyncrasy The patient with an underlying hypersensitivity state, receiving sulfonamide or penicillin therapy, should be observed carefully for the extremely rare occurrence of periarteritis nodosa We do not recommend chloramphenicol for long-term therapy, because of the possible development of agranulocytosis after its administration

E Management of Associated Paranasal Sinus Disease

Paranasal sinus disease may be responsible in many patients for reinfection and for the recurrence of cough and wheezing Vigorous attempts at eradication of sinus disease should be made, to prevent the irreparable sinobronchitic syndrome which often follows in its wake Most of these patients have been found to show allergic complications We have found Drihtol quite helpful—particularly when administered three or four times daily with the Vaponefrin nebulizer and nasal tips, by the air- or oxygen-powered technique

With evidence of frank purulent infection, 100,000 units of penicillin should be added to 1 cc of 1 per cent Neo-Synephrine and 1 cc o

1 per cent Pyribenzamine, with these aerosols administered nasally by the same technique. They generally appear to be well tolerated Postnasal drip with secondary cough is minimized, edema of the nasal mucosa is lessened, and restful sleep may follow

Penicillin treatment of the paranasal sinuses (by Proetz displacement) *through self-induced intranasal negative pressure may be quite* effective in certain patients. However, with the Venturi technique, suction and replacement of the secretions with penicillin aerosols may be employed with higher doses of penicillin and avoidance of damage to ciliary function This technique provides more uniform and diffuse mucosal application of the penicillin, and adequate penicillin blood levels.[16]

CHAPTER IX

The Use of ACTH and Cortisone

Adequate corticotropin or cortisone therapy often leads to reversal of many of the disturbances of pulmonary function observed in patients with chronic pulmonary emphysema secondary to chronic bronchial asthma [103] Corticotropin or cortisone produce far more improvement than conventional bronchodilators do in the *pulmonary* function of patients that have longstanding chronic bronchiolar obstruction with secondary emphysema [103] The hypothetical possibility of preventing the development of otherwise irreversible pulmonary fibrosis *by the periodic use* of corticotropin or cortisone is appealing, but such a gratifying result through the use of these hormones in the routine management of patients with chronic pulmonary emphysema of diverse etiology has not yet been observed by us The physician should seriously consider the brief use of these hormones for their secondary value, namely, as a stimulus to the patient's sense of well-being and appetite

We have administered approximately 150 courses of corticortropin to 100 patients with intractable bronchial asthma and 22 patients with chronic pulmonary emphysema and associated bronchospastic crises [145] We could not conclude that ACTH consistently rendered the cells or tissues immune to the effects of known antigens or that it affected the circulatory antibodies [139] [144] Furthermore, the remissive periods were of short duration in most patients [140]

I. Indications for the Use of Corticotropin

Pat...

chr

func ... disturbances cannot ... of corticotropin when reversi

morr...

... eventually becomes ... mind that the dominant defec ment of chronic cor pulmonale and its associated changes Whe hypoxia is not ameliorated through the use of bronchodilators, anti biotics, aminophyllin, intermittent positive pressure breathing in inspiration (IPPB/I), proper concentrations of oxygen, then an attempt should be made to bring about a prompt remission from the intractable bronchoconstriction with corticotropin or cortisone

The presence of cardiac failure associated with chronic cor pulmonale is not an absolute contraindication to the use of corticotropin or cortisone, provided that all the physiologic principles that have been outlined for the management of such failure (see Chapter VI) are taken into consideration. Although further retention of sodium and water, as demonstrated by hepatic or peripheral edema, occasionally may appear while corticotropin or cortisone is being administered, the relief afforded by these agents ...

... with corticotropin ... We have seen dramatic improvement ... failure secondary to chronic pulmonary emphysema and fibrosis in a patient bedridden with pulmonocardiac failure secondary to chronic pulmonary emphysema and fibrosis. After courses of corticotropin on two occasions, the patient was able to move about for three weeks and one week respectively. Unfortunately, the remissions were brief and death followed about six months after the first course of therapy.

It should be kept in mind that the patient with chronic pulmonary emphysema continually labors under the ...

... state may be noted after corticotropin therapy, manifested by euphoria, an increase in appetite and weight, a sense of well-being, reduction in pulse rate, etc.

The presence of peptic ulcer or active tuberculosis should be regarded as a contraindication to the use of corticotropin or cortisone in these patients. The presence of apparently inactive tuberculosis, however, is only a relative contraindication to the use of these agents. The use of these drugs may be followed by an exacerbation of the tuberculous infection. It is best to employ streptomycin and para-aminosalicylic acid therapy along with corticotropin or cortisone when these agents must be employed in patients with inactive tuberculosis. It is also advisable to employ streptomycin "coverage" for patients with underlying sarcoidosis. All patients receiving corticotropin or cortisone therapy, particularly those with proved, suspected, or potential tuberculosis, should have examination of their sputum and chest roentgenograms made frequently.

II. Methods of Treatment with Corticotropin

Short intensive courses of corticotropin should be employed when this form of therapy has been decided upon.

A. Intramuscular Schedule

After trial of several dosage schedules, we have adopted the following plan. An initial intramuscular dose of 40 mg. ACTHAR is repeated six hours later and followed by 20 mg. every six hours until maximal benefit has been observed for two days. By the fifth day of treatment the interval between injections can usually be increased to twelve hours. This dosage is continued until the time of discharge from the hospital. Patients occasionally require revision of this schedule. If eosinopenia does not develop after 100 mg. have been given, the dosage schedule is revised upward until the desired result becomes apparent.[140]

The total dose of a single course of therapy has varied from 240 mg. to 1070 mg., and duration of treatment from two and one half days to nineteen days. In general, our total doses have been larger than in other reported series. This may be explained partly by the fact that most of our patients are more seriously ill and partly by our conviction that prompt maximal and adequately persistent stimulation of the adrenal cortex is necessary for successful remissive therapy with corticotropin.

B. *Intravenous Schedule*

A continuous infusion of 5 per cent glucose in distilled water (3 liters per twenty-four hours, 30 drops per minute flow), is usually started with 0.5 gm. of aminophyllin per liter of fluid. ACTHAR is added, 10 mg per liter, and a total dose of 30 mg per twenty-four hours given for one or two days.[13] The eosinophils are usually found to be low or absent by the second day of this program. With improvement, the ACTH is then administered only in the first liter of fluid each day (10 mg daily), several days after the second day of continuous therapy. In the most severe cases, the infusion of glucose with aminophyllin is continued for a total of seven to ten days.

The resistance to the drug, and "eosinophil escape" that may occasionally be observed when corticotropin is administered intramuscularly can be overcome promptly with intravenous administration. With intravenous therapy the immediate results are usually more striking and the therapeutic effects more prolonged. The total dose, and thus the cost to the patient, may be reduced to one-fifth or one-eighth of that required when corticotropin is given intramuscularly. The hazards of treatment, however, particularly disturbances in psyche and potassium imbalance, are more pronounced with intravenous therapy, although it is our impression that several of the most effective remissions occurred in patients in whom disturbance in psyche were most prominent. This observation seems worthy of further study.

III. *Physiologic Changes and Side Reactions*

The usual physiologic alterations indicated by corticotropin have been observed in most of our patients but only rarely have they been severe enough to warrant cessation of intramuscular therapy or to contraindicate a second or third course of therapy. "Mooning" of the face, weight gain, psychic manifestations varying from elation to anxiety, eosinopenia, and subjective clinical improvement, have been noted more promptly with intravenous therapy. The tendency to salt and water retention in patients with frank or latent heart failure has been minimized by rigid salt restriction, digitalization, and the use of mercurial diuretics, and potassium chloride. Although it is possible to

reduce sodium and water retention in patients receiving ACTH the simultaneous administration of cation-exchange resins, Bonn has stressed that marked hypokalemia may occur in spite of pota sium supplements, thus precluding the use of these resins for thi purpose.[23] Potassium deficiency with marked muscular weakness confirmed by electrocardiographic and biochemical evidence, has been observed twice on the intravenous regimen. Routinely the patients are given 12 ounces of orange juice daily. Potassium supplements to prevent hypokalemia can be given also in the form of 15 minims of potassium iodide every six hours, or 2 Gm. of potassium chloride every eight hours.

Several patients complained of a sensation of tightness or mild constriction in the chest (similar to mild asthma). Abdominal bloating and a tendency to constipation were observed in a few patients. A very severe reaction to intramuscular therapy, characterized by pronounced dyspnea, orthopnea, cyanosis, confusion, and nonresponsiveness, was observed twice in the same patient. Another patient given intravenous therapy had two severe generalized convulsions with associated findings of low potassium levels. Skin reactions, a nonpruritic erythematous macular rash limited to the lower extremities, and generalized urticaria, have been observed in two patients. Three patients had febrile episodes following shortly after intravenous ACTH therapy, the pathogenesis of which could not be determined. Allergic reactions in the course of ACTH therapy may be successfully treated by the addition of oral cortisone for two or three days.

With the cessation of corticotropin therapy, occasionally there is a rapid recurrence of respiratory difficulties. We have attempted to prevent such recurrences, as well as to prolong the remissive state, by the administration of large doses of oral aminophyllin (Damite), or rectal aminophyllin and antibiotics, when indicated.

All of our patients while receiving ACTH are treated with penicillin or one of the broad-spectrum antibiotics to protect against the greater usceptibility to infection that may follow. A persistent type of ronchitis, generally responding to intensive antibiotic therapy, iodides, and antihistaminics, has been observed in many of our patients ho have received ACTH by both the intramuscular and intravenous utes.

This mechanism breaks down in a great number of pathologic circumstances, thus creating the hypoxic syndrome. Assuming that no alteration occurs in the circulation, the degree of hypoxia and the severity of its effects vary in accordance with the drop in arterial pO_2. The most important effects of hypoxia are on the respiration, the circulation, and the blood.

The effects of hypoxia upon the respiration of a normal man at rest are usually first manifested by tachypnea. This symptom develops only when the percentage of oxygen in the inspired air decreases more than 7 per cent, a smaller decrease producing no effect. Under severe exercise, these hypoxic individuals tend to increase their respiratory rate more rapidly, and hyperventilation usually accompanies such changes in respiratory rate.[102] Maximal response (up to 65 per cent increase in ventilation) occurs at about 22,000 feet above sea level when the arterial pO_2 falls to 30 mm. Hg, or when concentration of oxygen in the inspired air is only 6 or 7 per cent.[78] Respiratory changes of this kind are immediately followed by compensatory mechanisms, in which excessive excretion of carbon dioxide and consequent alkalemia serve as an effective buffering process that corrects the pH and thus prevents further hyperventilation.

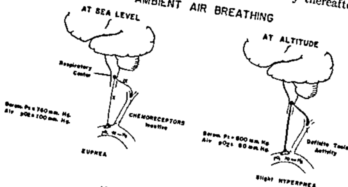
The important role of the chemoreceptor organs and the influence of the hypoxic stimulus has received considerable attention in recent years. The chemoreflex control of respiration under conditions of chronic hypoxia in patients with chronic pulmonary emphysema has been discussed in describing the carbon dioxide intoxication syndrome (see Chapter V).

Fig. 22 compares the effects of ambient air and of 100 per cent oxygen breathing on the centrogenic and chemoreceptor control of respiration in normal subjects at sea level and at altitudes.

At sea level the control of ambient air respiration is entirely centrogenic, due mainly to direct pCO_2 stimulation on the respiratory center. At altitudes, on the other hand, definite tonic activity of the chemoreceptors is brought about by the drop in arterial pO_2, and slight hyperpnea is then noted.

The effects of 100 per cent oxygen breathing at sea level are somewhat more controversial. Slight hyperpnea may occur in some individuals, probably as the result either of direct pO_2 stimulation on the respiratory center (centrogenic) or of bronchial irritation from the high

oxygen concentrations At altitudes, 100 per cent oxygen breathing is followed initially by hypoventilation, due to the abolition of the established chemoreflex drive for respiration Shortly thereafter, hy-



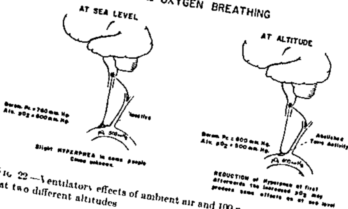


Fig 22 — Ventilatory effects of ambient air and 100 per cent oxygen breathing at two different altitudes

perpnea may be produced by the increased pO_2 which may act as described at sea level, producing hyperventilation

The effects of hypoxia on the circulation are manifested by an increase in heart rate, pulse, cardiac output, and venous return, these changes are associated with dilatation of the systemic blood vessels

and a decrease in peripheral resistance, which may finally lead to cardiac dilatation The blood pressure remains fairly constant whereas the resistance and flow in the pulmonary circulation tend to increase The implications of these changes have been discussed more fully under "Pulmonocardiac Complications" (see Chapter VI).

The effects on the blood are mainly (a) compensatory polycythemia (hypoxic erythrocytosis),[47] which in turn causes (b) an increase in blood volume and viscosity, (c) a decrease in coagulation time, and (d) a rapid increase in the amount of reduced hemoglobin (unsaturated hemoglobin) in the capillaries—and when this reaches a level of 5 Gm /100 cc of blood, cyanosis may be observed The low blood hemoglobin *concentration of severe anemia may* prevent the appearance of cyanosis In polycythemia, on the other hand, its presence is more readily noted

The effects of hypoxia on respiration, circulation, and blood being intimately related, play an integrated role in the development of complications in the emphysematous patient.

II. Classification of Hypoxia

In the main, classification of hypoxia follows the early ideas of Barcroft,[23] Haldane[78] and Best and Taylor,[26] with a few changes

A Hypoxic hypoxia can be brought on by the following causes (a) low oxygen tension in inspired air, (b) pathologic changes in any part of the respiratory apparatus, which prevents normal gas exchange, and (c) veno-arterial shunts. In this type of hypoxia, the arterial oxygen saturation and pO_2 are low

B Anemic hypoxia results from (a) hemorrhage or anemia, (b) poisons like carbon monoxide, nitrites and chlorates, which form stable compounds with hemoglobin. In this type, the normal red cells are not only reduced in number, but they individually give up a greater proportion of their oxygen, thus producing a pronounced fall in blood pO_2 In this form of hypoxia, there is a fundamental defect in the transport medium, hemoglobin, while alveolar oxygen tension *and gas exchange remain normal.*

C. Circulatory hypoxia or stagnant hypoxia may be present in the following circumstances. (a) circulatory failure, seen in classic con-

gestive heart failure and in severe metabolic disturbances in which the increased circulatory velocity cannot compensate for the high metabolic tissue needs (thyrotoxicosis, fever, etc), (b) obstruction of venous return (local anoxia), and (c) surgical shock Although the arterial oxygen saturation and content may be normal, the venous pO_2 tends to fall, because in the slower circulation through the dilated capillaries each red cell gives up more oxygen before reaching the peripheral tissues

D Histotoxic hypoxia results from poisons affecting the tissues and interfering with their oxidative processes Consequently, the venous blood carries back an oxygen content similar to the arterial Oxygen is available in adequate amounts and under normal tension but cannot be utilized by the tissues Cellular respiration may be interfered with directly by poisons such as the cyanides or through deficiency in a substance necessary for cellular respiration, as seen in certain infections or deficiency diseases

E Combinations of the various types of hypoxia are encountered These may be seen in chronic pulmonary emphysema with the alveolar-capillary block syndrome due to fibrosis, complicated by congestive heart failure Hypoxia of types A and C is found in these patients

III. Effects of 100 Per Cent Oxygen on Hypoxia

This discussion would not be complete without an interpretation of the physiologic effects of 100 per cent oxygen breathing in the hypoxic patient It can be described schematically as shown in Fig 23

Inhalation of 100 per cent oxygen increases the alveolar pO_2, thus making it possible for the blood to absorb and transport a quantity of gas greater than normal The hemoglobin saturation can be raised to practically 100 per cent, and the amount of oxygen physically dissolved in the plasma can be raised from 0 3 vol per cent to a maximum of 2 2 vol per cent This represents a possible increase of as much as 15 per cent in the oxygen-carrying capacity of the blood throughout the circulatory system, with a corresponding increase in the partial pressure available for the diffusion of oxygen from the blood into the tissues In this connection, Campbell and Poulton have demonstrated that the oxygen pressure in the tissues is increased proportionally

more than the oxygen content of the blood [31] The beneficial effects of increased pO_2 in blood and tissues are most noticeable in hypoxic patients In them, the oxygen saturation of the blood may increase from a level of 60 to 75 per cent or from a level of from 80 to 95 per cent when high concentrations of oxygen are inhaled

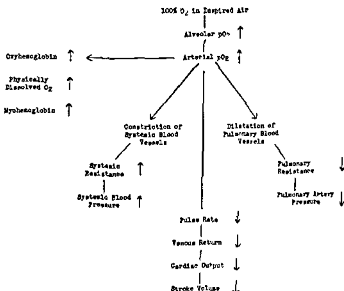


FIG 23 —Physiologic effects of 100 per cent oxygen breathing in the hypoxic patient

IV. *Methods of Administration of Oxygen*

The more frequently used methods of administering oxygen are by nasal or nasopharyngeal catheters, double nasal cannulae of rubber or metal, face masks, face tents, and various types of enclosing tents Each has advantages and disadvantages With these methods, oxygen can be given in concentrations of from 35 to 100 per cent Excellent reviews of the various types of equipment may be found in the papers of Boothby *et al*,[29] Barach *et al.*,[34] and also in manual and book form [3, 17, 139]

In selecting the type of equipment to be used, the physician must

consider the patient's physical and personal requirements as well as the concentration of oxygen desired

A Nasal Catheters For the routine management of manifestations of hypoxia, oxygen may be administered nasally by catheter or conjoined bent rubber or metal cannulae[8, 17] To employ the catheter technique properly, a soft latex rubber catheter designed for oxygen therapy (size No 10 or No 12 French), the tip lubricated with a water-soluble jelly, should be inserted into the nostril up to the posterior wall of the nasopharynx A concentration up to 38 per cent oxygen in the inspired air can be obtained with a 6 L, min flow of oxygen Placing the tip of the catheter opposite the glottis gives a slightly higher concentration, but the possibility that air may be swallowed and produce discomfort must be kept in mind The patient must be encouraged to breathe through his nose alone, or through his nose and mouth, but not through his mouth alone, so that he can obtain a higher concentration of oxygen in the inspired air Water humidification should be supplied Numerous other technical details are important Inadvertent plugging of some of the catheter orifices may result in mucous membrane "burns" from forceful flows through the patent orifices The catheter should be alternated from one side of the nose to the other at six hour intervals The hazards of frequent changing—nasopharyngeal irritation, middle ear and other secondary infections—and the potential hazards of pulmonary lipoid granulomata or chronic pneumonitis when oily lubricants are employed, should always be kept in mind

B Oxygen Tents and Hoods Various types of enclosing boxes, tents, and hoods—with or without open tops, and generally requiring ice chambers—have been devised for infants, children, and adults High flows of oxygen, or an air injector and lower flows of oxygen, are required to supply adequate oxygen concentrations and safe carbon dioxide accumulations

We have found the Permatent* to be a useful apparatus with further advantages in its low cost and sturdy construction capable of withstanding more than the average hospital abuse[18] It is made of clear, heavy-gauge, vinyl plastic with adequate zippered entrances to the ice compartment and the patient The ice compartment tilts safely as the patient assumes a more vertical position The patient's head is

* Manufactured by Pilot Medical Plastics, Inc , Lynn, Mass

comfortably enclosed in an expansible neck collar that is adjustable There are two front portholes for the egress of carbon dioxide or admission of increased concentrations of water vapor, or antibiotic or bronchodilator aerosols, the top of the tent also can be opened to any desired degree. Proper degrees of humidification or dehumidification can be obtained With oxygen flows of from 10 to 14 L./min., the oxygen concentrations in the tent range from 50 to 70 per cent; carbon dioxide accumulations, determined in our laboratory, have been consistently below 1 00 vol per cent.

The new type of "iceless" oxygen tent (a refrigerated, humidity-controlled, and air-conditioned unit) which encloses the entire bed by means of a transparent canopy, is a comfortable and effective means of administering oxygen in concentrations of from 40 to 60 per cent. Gas studies of one of our subjects receiving oxygen at 12 L/min in one of these tents revealed concentrations of 40 per cent oxygen and 0 85 per cent carbon dioxide at the end of thirty minutes, and 43 82 per cent oxygen and 1 04 per cent carbon dioxide at the end of sixty minutes The freedom of motion and the uninhibited feeling of being able to see all that goes on is appreciated by the patient. To achieve this ideal, however, requires not only costly apparatus and adequate technical care, but continuous oxygen flows of at least 12 L/min. Unfortunately, with most of the oxygen tent installations employed, the desired oxygen concentrations are not obtained. This form of therapy, although ideal when correctly employed, should be reserved for special situations only.

C Oxygen Masks When the problem calls for the administration of high concentrations of oxygen, a suitable mask should be used Two well known types of apparatus are available, namely, the BLB mask[29] and the Meter Mask [14] With the latter, an air injector (concentration meter) is utilized to deliver the desired concentrations of oxygen (from 40 to 95 per cent) Humidification may be employed Positive pressure breathing in expiration may also be used, if indicated, by a metering disk in the Meter Mask, the Respirator Aids Mask uses a glass tube set in a water bottle, for the same purpose

These masks are comfortable for some patients To many others, their continuous use becomes objectionable The proper maintenance of these masks must be carefully supervised to achieve the results they are capable of producing The Meter Mask is a distinct credit to the ingenuity of its originators.[17] Rebreathing, carbon dioxide ac-

cumulations, and negative pressures in the face piece are not encountered with this apparatus It is of tremendous practical value when high concentrations of oxygen are indicated, as well as for short periods of helium-oxygen breathing in patients with severe bronchoconstriction Positive pressure oxygen therapy applied in the expiratory phase of respiration IPPB-(E)-Meter Mask (see Chapter



Fig 24 – Plastic oxygen face tent

XI) can be given with this apparatus for treating various types of pulmonary edema

D A New Type of Face Tent Some of the undesirable features of the nasopharyngeal catheter and those of the more complex rubber face masks and oxygen tents can be eliminated by using the new type of oxygen face tent* (see Fig 24), designed for the routine administra-

* ABC Oxygen Face Tent manufactured by Eliot Medical Plastics, Inc Lynn, Mass

tion of oxygen in adequate concentrations for either brief or prolonged periods [142]

The tent fits comfortably over the lower portion of the patient's face, opening wide at the forehead for easy egress of exhaled gases and vapors It is made of flexible clear plastic, adjusts to various face sizes by means of its forehead and head straps, and weighs only 1¼ ounces It has simplicity of operation and maintenance and is easily removed for general nursing care and feeding No constant attendance or expert supervision is necessary. When indicated, feeding through the Miller-Abbott tube or simultaneous Wangensteen suction drainage can be carried on simply The face tent may be sterilized by soap and water cleansing followed by the use of an aqueous detergent antiseptic or Zephiran

Humidified oxygen enters the face tent through a shower-head dispersal system that eliminates some of the discomforts noted with nasal catheters and face masks Continuous oxygen flows replace the consumed oxygen, and the carbon dioxide and warmed vapors flow out easily through the open top of the face tent The movement of the air-oxygen mixtures through the open top, along with the oxygen flows entering the mask, are sufficient to dilute the patient's carbon dioxide output to safe levels Breathing is completely free and the visibility is unobstructed at all times Patients do not complain of claustrophobia or a sense of suffocation, nor of the smell and sensation of rubber near them, as noted by some when the usual face masks are employed Instead, a cooling sensation is generally felt over the entire oronasal region.

With this oxygen face tent and a 6 L/min flow, there is no concern about the possibility of oxygen toxicity More than 150 determinations of oxygen and carbon dioxide concentrations in the inspired air were made at the end of five minutes, thirty minutes, and one hour of oxygen breathing with oxygen flows set at 4, 6, and 10 L/min The oxygen and carbon dioxide determinations were made in the Scholander apparatus, with gas samples obtained by syringe from directly in front of the nasal orifices at the start of inspiration. The oxygen concentrations in the inspired air ranged consistently between 40 and 70 per cent. The highest oxygen concentrations were obtained with 10 L/min flows In the 150 determinations, the carbon dioxide concentrations averaged 1 08 per cent. The summary of these observations appears in Table 5

Flows of 5 or 6 L/min are adequate to assure oxygen concentrations ranging from between 40 and 55 per cent in the inspired air and allow proper elimination of carbon dioxide. With the higher flow, greater inspired oxygen and lower carbon dioxide concentrations are obtained, and the cooling sensation over the oronasal region is intensified.

TABLE 5.—*Average Concentrations of O_2 and CO_2 at 4-6 and 10 Liter per Minute Flows of O_2 Obtained during a One Hour Period in the "Oxygen Face Tent"*

No. Patients	No. Determinations	O_2 Flows per Min (Liters)	O_2 Concentration	CO_2 Concentration
2	12	4	47.59	1.43
5	30	6	52.27	0.99
3	18	10	53.71	0.84

V. Reactions to the Use of Oxygen

There are several types of intolerance to oxygen that should be kept in mind.

A. One form, chiefly characterized by signs of pulmonary irritation and substernal soreness, may be observed in *normal* subjects after the continuous inhalation of oxygen concentrations above 95 per cent for periods longer than twelve hours.[17, 35]

B. Patients with *hypoxia* who receive concentrations of over 95 per cent oxygen *without* interruption over long periods of time may also have signs and symptoms of pulmonary irritation. Actually, although this is theoretically possible, it is hardly likely with mask therapy which is by necessity interrupted. There is ample clinical and experimental evidence that concentrations of oxygen between 50 and 70 per cent may be used for long periods without damage to the lungs of the hypoxic patient.[19, 44]

C. Another type of "oxygen intolerance" may be observed in patients who are inadvertently inhaling excessive concentrations of carbon dioxide (more than 1.5 per cent) for long periods while receiving adequate oxygen therapy. This occurs in patients given oxygen by mask or tent, when the flow of the oxygen is adequate to correct the hypoxia but inadequate to wash out the accumulated carbon dioxide. This is particularly apparent when rebreathing-bag systems are used in mask therapy. Under these conditions, stimulation of respiration

and other disturbances of the central nervous system may be seen as toxic manifestations of carbon dioxide excess

D The hazards of employing oxygen in concentrations above 50 per cent in patients with chronic pulmonary emphysema and pulmonary heart disease have long been recognized. The syndrome of carbon dioxide intoxication and respiratory acidosis, previously described, may be observed in these patients after the injudicious use of oxygen The sudden administration of high concentrations of oxygen is tolerated poorly Although clearing of the cyanosis may follow, unfortunately it may be accompanied by distressing central nervous system symptoms culminating in coma The pathogenesis and treatment of this syndrome have been discussed in Chapter V.

CHAPTER XI
Mechanical Respiration

The therapeutic value of mechanical respiration in acute a chronic pulmonary diseases, as well as in cardiac conditions, has e couraged numerous investigations of the underlying physiolog mechanisms involved, on which the rational use of this treatme must be based Through the years many types of apparatus fo mechanical respiration have been tried, some have had to be aban doned because of unexpected complications A variety of such equip ment may be found in the storerooms of physiologists and clinicians interested in pulmonary diseases.

I. Pressure Breathing

The numerous mechanical devices successfully used for pressure breathing include face masks, hood-domes, and body respiratory chambers Depending on the method of application, these devices induce different physiologic responses

A Notation System in Pressure Breathing

The factors that enter into all types of pressure breathing are.

1. Timing of Pressure
   a) Intermittent—during inspiration or expiration
   b) Continuous—during inspiration and expiration

and other disturbances of the central nervous system may be seen as toxic manifestations of carbon dioxide excess.

D The hazards of employing oxygen in concentrations above 50 per cent in patients with chronic pulmonary emphysema and pulmonary heart disease have long been recognized The syndrome of carbon dioxide intoxication and respiratory acidosis, previously described, may be observed in these patients after the injudicious use of oxygen The sudden administration of high concentrations of oxygen is tolerated poorly Although clearing of the cyanosis may follow, unfortunately it may be accompanied by distressing central nervous system symptoms culminating in coma. The pathogenesis and treatment of this syndrome have been discussed in Chapter V

CHAPTER XI
Mechanical Respiration

The therapeutic value of mechanical respiration in acute and chronic pulmonary diseases, as well as in cardiac conditions, has encouraged numerous investigations of the underlying physiologic mechanisms involved, on which the rational use of this treatment must be based Through the years many types of apparatus for mechanical respiration have been tried, some have had to be abandoned because of unexpected complications A variety of such equipment may be found in the storerooms of physiologists and clinicians interested in pulmonary diseases

I. Pressure Breathing

The numerous mechanical devices successfully used for pressure breathing include face masks, hood-domes, and body respiratory chambers Depending on the method of application, these devices induce different physiologic responses

A Notation System in Pressure Breathing

The factors that enter into all types of pressure breathing are:
1. Timing of Pressure
   a) Intermittent—during inspiration or expiration
   b) Continuous—during inspiration and expiration

and other disturbances of the central nervous system may be seen as toxic manifestations of carbon dioxide excess.

D The hazards of employing oxygen in concentrations above 50 per cent in patients with chronic pulmonary emphysema and pulmonary heart disease have long been recognized. The syndrome of carbon dioxide intoxication and respiratory acidosis, previously described, may be observed in these patients after the injudicious use of oxygen The sudden administration of high concentrations of oxygen is tolerated poorly Although clearing of the cyanosis may follow, unfortunately it may be accompanied by distressing central nervous system symptoms culminating in coma. The pathogenesis and treatment of this syndrome have been discussed in Chapter V.

CHAPTER XI
Mechanical Respiration

The therapeutic value of mechanical respiration in acute and chronic pulmonary diseases, as well as in cardiac conditions, has encouraged numerous investigations of the underlying physiologic mechanisms involved, on which the rational use of this treatment must be based Through the years many types of apparatus for mechanical respiration have been tried, some have had to be abandoned because of unexpected complications A variety of such equipment may be found in the storerooms of physiologists and clinicians interested in pulmonary diseases

I. Pressure Breathing

The numerous mechanical devices successfully used for pressure breathing include face masks, hood-domes, and body respiratory chambers Depending on the method of application, these devices induce different physiologic responses

A. Notation System in Pressure Breathing

The factors that enter into all types of pressure breathing are.
1. Timing of Pressure
   a) Intermittent—during inspiration or expiration
   b) Continuous—during inspiration and expiration

2 Type of Pressure
   a) Positive—greater than atmospheric pressure
   b) Negative—less than atmospheric pressure
3 Site of Pressure
   a) Airway passages
   b) Chest wall

For the sake of simplicity in our discussion of pressure breathing, we are abbreviating key terms in this list by reducing the component words to their initial letters The notation is summarized in Table 6 (For example, the term *Intermittent Positive Pressure Breathing in the Inspiratory Phase* employing the Bennett valve will appear as IPPB/I —Bennett)

TABLE 6 —*Pressure Breathing Notation System*

Timing	Type	Pressure Breathing	Phase of Respiration	Notation: Code	Notation: Device
I*	P†	PB	/I‡	IPPB/I	Bennett Valve—e g
I	P	PB	/E	IPPB/E	Meter Mask—e g
I	N	PB	/I	INPB/I	Body Respirator
C	P	PB	/I & E	CPPB/I & E	Hood—Dome
C	N & P	PB	/I & E	C(N & P)PB/I & E	Body Respirator

* C = Continuous, I = Intermittent
† P = Positive, N = Negative
‡ /I = Inspiratory, /E = Expiratory

B. *Methods and Equipment*

Timing

There are two modes of administering pressure breathing, the gas is either intermittent or it is continuous.

In the *intermittent* type of positive pressure breathing, the gas mixture is supplied in either the inspiratory (IPPB/I) or expiratory (IPPB/E) cycle, usually through a face mask. Of the several types of mask devices that supply IPPB, those most commonly used for IPPB/I alone incorporate the Burns, Mines Safety Appliance, Emerson, or Bennett valves These valves are automatic, flow- or pressure-sensitive cycling devices, with varying advantages especially related to the type of mask pressure curves that they supply For IPPB/E only, the Meter Mask[17] and the Respiration Aids Mask are used

The patient sets up a gentle positive pressure in expiration by blowing the expired air through the narrowed orifices of the metering disk (See Chapter X on "Oxygen Therapy")

The body respirators—Drinker, Collins, or Emerson—are useful for supplying *a form of* INPB/I, *applied to the chest wall*, a negative pressure is produced within the chamber during inspiration, whereas expiration is passive In addition, if considered desirable, the passive expiratory phase may be converted to a positive one, thus establishing a continuous type of pressure breathing negative in inspiration and positive in expiration—C (N & P) PB/I & E—Emerson Barach and his associates recently described a device that permits inspiration at atmospheric pressure and expiration at a negative pressure of from 5 to 20 mm Hg (INPB E)[19] Presently they are employing a manually controlled cycling valve, in conjunction with a motor unit and face mask This permits inspiratory positive pressure with an extremely rapid change to an expiratory negative pressure A high expiratory volume flow rate is noted. Effective coughing has been obtained in patients with retained pulmonary secretions[21]

Special features added to the conventional tank respirator permits its use as a cough chamber[20] A negative pressure of 40 mm Hg (54 cm water) is gradually developed in the chamber by a motor blower unit in a period of 2 5 seconds Sudden release of this inspiratory negative pressure is accomplished in only 0 06 seconds by the opening of a 5-inch butterfly valve The swift change in pressure (from minus 40 mm Hg to atmospheric pressure) produces a high rate of expiratory flow, equivalent to that produced by a moderately vigorous cough in a normal person[20] The mechanism is called exsufflation

The continuous method of pressure breathing supplies air, oxygen, or a mixture of helium and oxygen under positive pressure during both the inspiratory and expiratory cycles (CPPB/I & E) The positive pressure enclosing hood apparatus or the double-bellow mask (O E M) may be employed for this purpose[17] The hood requires a tight neck closure, a cooperative patient, and considerable technical help for proper management The patient frequently objects to the double-bellow mask because of the sense of forced breathing in the expiratory phase, in its present form, furthermore, the equipment requires considerable technical care and readjustment of valves.

C. Physiologic Data

Essentially, the use of pressure breathing is based on the creation of a pressure gradient from the mouth down to the pleural space. In the inspiratory phase in normal individuals, positive pressure through a face mask produces mechanical inflation of the lungs similar in some respects to that produced by negative pressure around the thorax by means of the body respirator. At the height of inspiration, however, the pressure built up in the patient's airway is greater than that built up around the body.[106]

In the expiratory phase, negative pressure by mask normally has the same mechanical and physiologic effects on respiration and circulation as positive pressure exerted by the body respirator—provided, of course, that these counterforces are of equal magnitude.[106, 107, 172]

In essence: during inspiration, positive pressure by mask is comparable to negative pressure by body respirator; during expiration, negative pressure by mask is comparable to positive pressure by body respirator—*normally*. In the emphysematous patients these pressures may not be transmitted as exact equivalents since the equilibrium of the elastic and coordinating structures have been upset by the uneven damaging of intermediate tissues.

The problem of overcoming the physiologic resistance in the bronchial tree has to a large extent been solved by improved types of pressure breathing apparatus. Insofar as pressure breathing accomplishes an increase in lung volume, it decreases bronchial resistance. Clinical, roentgenologic, and physiologic studies have made it clear that (1) the bronchi become elongated and distended during the inspiratory phase, and (2) the bronchi become shortened and constricted during the expiratory phase. Bronchial resistance can therefore be diminished by practicing respiration at a higher inspiratory midposition. Pursuing this concept in physiologic studies of bronchial resistance as reflected in the intra-alveolar pressure in normal individuals, Maloney *et al.* determined the effects of breathing at different thoracic midpositions and compared the results to the results effected by pressure breathing.[105] The same results should be obtainable in any individual who is physiologically able to increase his lung volume voluntarily. If the emphysematous patient loses the power of creating an effective pressure gradient between the lung and

pleura—despite carrying on respiration at a high thoracic midposition—it is our impression that he can re-establish this gradient if he is subjected to positive pressure breathing employing pressures higher than the 5 cm. of water utilized by these investigators in their experiments

Bronchial secretions, usually thick and tenacious, accompanying a dry and ineffective cough that exhausts the patient (tussic insufficiency), can become converted to a thinner, less tenacious type with IPPB/I treatments Motley and Tomashefsky[117] state that with this type of pressure breathing there is no danger that the secretions will be aspirated, as one might assume at first thought, since IPPB/I establishes a gradient in the velocity of air displacement in and out of the lung Their results measured in instantaneous recordings of flow rate under fast breathing show that the peak expiratory velocity is higher than the peak inspiratory velocity, and therefore the expulsion of these secretions is facilitated [117]

Poor intrapulmonary mixing and faulty distribution (defective ventilation-perfusion relationship) are greatly corrected by IPPB/I, as shown by reduction in residual volume, increase in alveolar and arterial blood pO_2, and decreases in aeration gradient, transfer gradient, and arterial blood pCO_2.[118] Careful evaluation of these observations helps us to understand the invariably better results obtained with a bronchodilator when its administration is through IPPB rather than through hand-bulb nebulizations or air- or oxygen-powered aerosols

The chronic emphysematous patient whose efficiency of intrapulmonary mixing is highly impaired cannot rely exclusively on his own inspiratory effort The beneficial effects of IPPB/I have been attributed to the following physiologic processes.

(1) The improvement in distribution of inspired air, particularly to the bases of lung

(2) The opening of all available alveoli (more uniform alveolar aeration)

(3) More rapid air displacement through reduction of bronchial resistance

(4) Reduction of residual air volume—which may not, however, be observed or become apparent until after several months of treatment

The physician should be cognizant of the effects that pressure breathing has on the peripheral circulation as well as on the heart. The cardiac output is a true equivalent of the venous return, which in turn depends on the gradient between the peripheral venous pressure and the pressure in the right auricle Although the cardiac output must be equal for both ventricles in a compensated heart, it becomes physiologically unequal when deep breathing or a Valsalva-like maneuver creates a differential output and pressure between the pulmonary and systemic circulation. For all practical purposes, these variations can be understood if the behavior of the right ventricular output is understood When IPPB is applied through the mouth by means of a mask, the cardiac output tends to fall during the pressure phase of the cycle, while the net filling pressure of the right ventricle also falls The opposite holds true for the phase of decreasing mask pressure.[44]

The following sequence of events is likely to develop The increased intrathoracic pressure (see Fig. 25A) at first "squeezes" the lungs, momentarily increasing the blood return to the left ventricle and raising its output. This in turn increases the systemic pulse pressure for the first 4 or 5 beats, (see Fig. 25B) but it decreases immediately afterward. At the same time, the venous return is slowed, damming a considerable amount of blood and decreasing the right ventricular output The pulmonary arterial pressure rises, while its pulse pressure drops throughout the period (see Fig. 25C) If the intrathoracic pressure is not released after from 30 to 40 seconds, however, tachycardia and peripheral vasoconstriction tend to elevate the venous pressure These compensatory mechanisms originate in the pressoreceptors of the carotid sinus and travel through the ninth nerve to the sympathetic centers The intrathoracic positive pressure, which is still acting, cannot prevent the "escape-like" type of mechanism whereby cardiac output is returned to normal *The physiologic changes in the pulmonary and systemic artery pressures are far more important* In the process of this "escape," they not only return to normal but "overshoot." (See Fig. 25D.)

Positive pressure breathing, when utilized for therapeutic purposes,

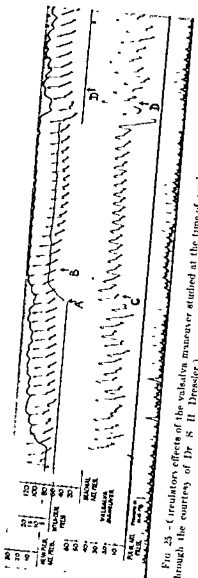


FIG 25 – Circulatory effects of the valsalva maneuver studied at the time of cardiac catheterization (Reprinted through the courtesy of Dr S H Dressler)

does not maintain increased intrathoracic pressures for very long periods, and the induced changes in cardiac output will depend [illegible]

start of expiration The expiratory cycle must be longer than the inspiratory one The type III curve provides adequate time for compensation of the inspiratory drop in cardiac output. This is accomplished during expiration through a lowering of intrapleural pressure while the right ventricular net filling pressure increases. Even under acute experimental conditions, normal individuals will react against transient falls in cardiac output by reflex peripheral vasoconstriction applied to the venous system, aiming to reconstitute the venous gradient.[172] The presence of normal sympathetic pathways are therefore necessary to permit the "escape-like" type of mechanism previously described

IPPB/I providing the Type III curve, is most useful for the treatment of the hypoventilation syndrome. In some patients with chronic pulmonary emphysema—where effective ventilation is highly diminished and in whom the sudden administration of high *concentrations of oxygen* would lead as it commonly does, to the carbon dioxide intoxication syndrome—adequate correction of the hypoventilation seems by far the most important single therapeutic procedure

Most gratifying clinical results with IPPB/I were observed in a patient (*C P.*) who, in addition to chronic pulmonary emphysema and the carbon dioxide intoxication syndrome, had cardiac failure Manifestations of the carbon dioxide intoxication syndrome had been noted several times in this patient during injudicious administrations of high concentrations of oxygen just prior to this study

As can be seen in Table 7, this patient was subjected to six consecutive hours of IPPB/I, utilizing room air. Starting from the control point (Table 7, IIIa), it can be seen that the rise in minute ventilation was sufficient to correct the increased arterial pCO_2 and restore the pH to normal levels (Table 7, IIIc). These values had been thrown out of balance by previous administrations of high oxygen concentrations that had been given specifically to show his susceptibility to respiratory acidosis (Table 7, IIb)

For experimental purposes, on a subsequent day, 100 per cent oxy-

TABLE 7 —*Correction of Respiratory Acidosis with Intermittent Positive Pressure Breathing*

	Min Vent (L/min)	R R	Pulse	Arterial Blood*					
				pCO_2 (mm Hg)	pO_2 (mm Hg)	Buf Base (mEq/L)	O_2 Sat (%)	Chloride (mEq/L)	pH
I a) Control 8 45 A M	5 500	16	88	69	40	63	74 58	92	7 40
b) 5% CO_2, 95% O_2 at 2L flow for 7 min	5 300	17	80	63	62	61	89 48	92	7.40
II a) Control		17	82						
b) 100% O_2 for 72 min	3 300	22†	84	89	76	59	91 83	93	7 28
III a) Control	3 300	22	84	89	76	59	91 83	93	7 28
b) *IPPB* Compr Air 15 cm H_2O, 2 hrs	8 400	18	84	72	59	60	85 69		7 35
c) At six hours		10	84	65	49	61	82 94	97	7 39

* Hematocrit—40%

† Shallow

gen was given to this patient by means of IPPB/I—Bennett. No harmful effects were observed. The above experiments demonstrated the following: first, the therapeutic effects of IPPB/I, utilizing room air, in the management of respiratory acidosis, and second, the protection afforded by IPPB/I against respiratory acidosis when oxygen is necessary. When prolonged IPPB/I therapy is to be employed in critically ill patients, as for example, in respiratory acidosis or severe pulmonary edema, it should be interrupted at the end of each hour for 30-minute rest periods.

The beneficial effects of positive pressure breathing in the treatment of acute pulmonary edema were clearly described by Barach and his associates.[12, 13] They devised two types of apparatus for providing positive pressure (see Chapter X): during both phases of the respiratory cycle (CPPB/I & E—Hood); and the other, during expiration alone (IPPB/E—Mask).[17] Signs of pulmonary edema rapidly disappear when pressure is applied, the gentle internal distending force serving to keep the bronchioles patent while opposing the hydrostatic pressure within the capillaries. Barach compares this to the effects of putting a finger on the capillary wall itself. Other modifications in circulatory function, particularly a diminution in the flow of blood into the right side of the heart, allow more time for the failing left ventricle to pump the pulmonary vascular bed free of excess blood. The lowering of the cardiac output is related to the mean applied intrapulmonary pressure.[20] These modifications are similar to those derived through application of a tourniquet to the extremities. A narrowing in the transverse cardiac diameter is also roentgenographically evident after the application of high mask pressure.[17]

Patients with peripheral circulatory collapse, as in hemorrhagic shock, should not be injudiciously exposed to positive pressure breathing. Peripheral vasoconstriction in these patients has already been utilized to a maximum extent, and a further drop in cardiac output is all that can be expected. In emphysematous patients, however, when there is evidence of shock or loss of the vasoconstrictor mechanism, IPPB/I combined with a negative expiratory phase pressure will help reconstitute the venous gradient and cardiac output as well as prevent a further drop in blood pressure.[19, 105] Similar results can be obtained through application of changing pressure on the chest wall with a body respirator—C(N & P)PB/I & E-respirator.

From the foregoing it will be seen that positive pressure breathing tends to accomplish the following: (1) Overcomes the bronchial resistance and widens the bronchi (2) Helps establish a more efficient cough. (3) Creates a more uniform alveolar aeration, thus improving intrapulmonary mixing (4) Reduces residual volume (5) Improves the ventilation-perfusion relationship by virtue of the effects noted in (3) and (4) (6) Prevents or minimizes the outward filtration through the capillary membrane (7) Diminishes the blood volume returning to the right side of the heart, with a subsequent drop in cardiac output and blood supply to the lungs

D The Use of Intermittent Positive Pressure Breathing—Inspiratory

The Bennett valve produces an ideal physiologic type of mask pressure curve (Type III) through the action of a cycling valve, that allows the patient to exhale for as long as he wishes [41] The patient completely controls the cycling of the valve by his own respiratory rhythm. The rate of instantaneous inspiratory flow, which may exceed 100 L/min places no limitation on whatever the breathing pattern may be—whether of the dyspneic, the acute asthmatic, or the cardiac patient A uniform low mean mask pressure for the entire cycle is achieved by a slow building-up of pressure in inspiration (the peak usually adjusted at from 10 to 20 cm of water) and an early drop in expiratory pressure which is continued for as long as the patient requires (always longer than inspiration) Several gas mixtures may be employed air, helium-oxygen, or 100 per cent oxygen For routine use, air or 100 per cent oxygen is satisfactory, in the carbon dioxide intoxication syndrome, air or helium-oxygen is preferable

An adequate program for most patients with chronic pulmonary emphysema is a course of therapy for from three to four weeks, consisting of three treatments daily, each treatment lasting from fifteen to twenty minutes [72] We usually employ a bronchodilator along with a detergent agent that lowers surface tension, such as aqueous Zephiran 1:1000, Duponol or Alevaire, to induce relief from bronchoconstriction and diminish the viscosity of the sputum After brief training, most patients are able to discard the face mask and breathe through a simple mouthpiece attached to the apparatus

If there is any suspicion of coronary heart disease, it is advisable to use oxygen instead of room air in positive pressure breathing. It has been shown that the use of oxygen in such patients will prevent electrocardiographic changes in the T waves and S-T segments [illegible]

E Results with Intermittent Positive Pressure Breathing—Inspiratory—Bennett Valve

Along with other investigators, we have found IPPB/I an effective aid in the treatment of chronic pulmonary emphysema [72, 116, 151] An increase in the volume of ventilation is accompanied by a decrease in breathing resistance Pneumotachograms also show changes consistent with improvement in the elasticity of the lung parenchyma.[117] With IPPB/I and bronchodilator aerosols, the average improvement in the maximal breathing capacity is about 20 per cent, the greatest being observed in the severer degrees of emphysema [72] The effect on the vital capacity follows a similar pattern of improvement, with the greater benefit in severer emphysema even more pronounced [72] Gordon emphasizes the superiority of bronchodilator drugs given with IPPB/I over the same bronchodilators used alone. Instead of the 20 per cent improvement in maximal breathing capacity averaged with IPPB/I and aerosols, the same group of patients averaged only a 10 per cent improvement when they used the same bronchodilator by hand nebulization [72]

Favorable results with IPPB/I—Bennett were recently reported by Smart *et al* [151] Improvement followed IPPB/I in 77 per cent of their series of 167 emphysematous patients; judged on the basis of increased exercise tolerance, easier breathing, and decreased wheezing, the vital capacity improved 84 per cent and the maximal breathing capacity improved 76 per cent. Bronchial drainage, an important factor in these patients, was uniformly increased during the first week of treatment The quantity of secretions tended to decrease thereafter. Diaphragmatic motion, as visualized by fluoroscopy, improved

If the function of the lung may be defined as a mechanism essentially admitting oxygenation and eliminating carbon dioxide, adequate information on the overall efficiency of the various methods of supplying pressure breathing in pulmonary disease should be

estimated by determinations of these gases in the arterial blood. In our experience, IPPB/I—Bennett has proved itself. With this apparatus, the administration of either oxygen or compressed air for adequate periods of time results in a considerable rise in arterial blood oxygen saturation and an adequate excretion of carbon dioxide. The case of patient C. P., previously discussed, is illustrative. Our results are in agreement with Motley's observations on chronic pulmonary emphysema in coal miners. He explains the improvement in his cases on the basis of a decrease in the aeration gradient (early factor in the physiopathologic changes) and the subsequent decrease of the transfer gradient. (See Chapter III.) Although the aeration gradient is truly representative of pure ventilatory function, the transfer gradient introduces the concept of blood gas exchange. With a more effective alveolar ventilation, the transfer gradient tends to decrease, reflecting the improvement in the gas exchange. In this connection, IPPB/I represents a quick and reliable guide for differentiating between the roles respectively played by venous admixture and the membrane diffusion component. Both of these factors affect the transfer gradient. (See Chapter III.) If the transfer gradient failed to decrease after IPPB/I therapy, it would indicate predominance of the membrane diffusion abnormality over the venous admixture component.[114]

It must be stressed that this type of treatment cannot be expected to reverse anatomic damage pre-existing in the respiratory system. What we can expect from IPPB/I is increased physiologic utilization of the pulmonary reserve and, in some cases, periods of remission in the otherwise inexorably progressive disease.

F. *Body Respiratory Chambers*

Tank respirators of the Drinker, Emerson, or Collins type should be used for artificial respiration to combat the hypoventilation in drug depressions or respiratory acidosis. Supplemental oxygen can be provided by catheter or face mask. The major problem is the difficulty of synchronizing the patient's respirations with the cycle of the respirator; constant nursing care is involved. The new Emerson respirator cycles automatically with the patient's breathing.

II. Electrophrenic Respiration

The hypoventilation observed in patients seriously ill with chronic pulmonary emphysema, and possibly contributed to through injudicious use of high concentrations of oxygen, may be temporarily reversed by the use of electrophrenic respiration, although this procedure is not suitable for prolonged treatment The use of this method is based on the following principles[133]: (1) Phrenic stimulation momentarily suppresses the disordered impulses that may come from a damaged respiratory center. (2) It does not impair cardiac output since the venous return in inspiration is augmented by a reconstruction in the negative intrapleural pressure and also because blood is effectively squeezed from the abdominal viscera by diaphragmatic contraction [1] (3) It tends to maintain blood pressure.[172] The stimulation of only one phrenic nerve is enough to ventilate both lungs: ventilation of the contralateral lung will follow in the wake of the mediastinal shift and diaphragmatic descent.

CHAPTER XII

Pneumoperitoneum Therapy

Considering emphysema as basically a state where the lungs are hyperinflated and alveolar ventilation is ineffective, pneumoperitoneum has proved to have valuable effects, related to the reduction in volume of those components of the total lung capacity which interfere with gas exchange In recent years several groups of investigators have employed this form of therapy successfully in significant numbers of patients with chronic pulmonary emphysema[15, 66, 121, 177]

I. Physiologic Basis for Pneumoperitoneum Therapy

Although we are unable to explain all the mechanisms by which pneumoperitoneum is effective, physiologic and clinical studies are of great value in determining the indications for this procedure Stretching of the diaphragm from a flat position to one that permits a more efficient performance is the first step in inducing favorable changes in the bronchopulmonary apparatus. Statically considered, after pneumoperitoneum the bronchial tree apparently is rearranged to a more efficient position, whereby secretions find their way out with less effort on the part of the patient Dynamic restoration of the diaphragmatic motion follows in the wake of this static correction, and pulmonary ventilation subsequently improves

The importance of this relationship is well illustrated by observations on the use of phrenic nerve interruption for the treatment of pulmonary tuberculosis. Further drastic reduction of the pulmonary function already impaired in these patients (sometimes up to 60 per cent) usually follows the artificial diaphragmatic paralysis.

We must emphasize that improvement of diaphragmatic function is an important accomplishment because the diaphragm represents for many emphysematous patients the only structure available for carrying on pulmonary ventilation. Following effective treatment, improvement in intrapulmonary mixing has been demonstrated, as well as a decrease in functional residual capacity and residual volume, and in the ratio of residual volume to total lung capacity.[66, 93, 175] These results, however, should not be expected in patients with pneumoconiosis where pulmonary fibrosis predominates,[116] or in patients with emphysema complicated by multiple bullae or giant cysts,[32] unless pneumoperitoneum is combined with other procedures.

Improvements in vital capacity and in maximal breathing capacity are not necessarily correlated with each other. The latter, representing a more stress-dynamic function test, may show changes in either direction, depending upon the underlying pathologic changes responsible for the chronic pulmonary emphysema. Improvement in ventilatory function will be reflected thereafter in more adequate gas exchange. As time goes on, the improved gas exchange will bring about a higher arterial oxygen saturation and consequently a decrease in carbon dioxide content and partial pressure.

The recent observation of Kory *et al.* is of importance in relation to the *effect of pneumoperitoneum* upon circulatory dynamics.[82] Cardiac output was consistently decreased (10 to 30 per cent), and in one patient with cor pulmonale institution of pneumoperitoneum was followed by a decrease in the elevated pulmonary arterial pressure. These results may be related to the correction of the hypoxia.

Clinically, such patients show varying degrees of improvement. In many the cough becomes more productive, and they are able to evacuate a greater volume of bronchial secretion. The reduction in residual volume brings about a more efficient alveolar ventilation. Less dyspnea is noted, and tolerance increases toward mild exercise. In general, improvement in appetite results, and a weight gain may be noted. Such patients rest better and sleep better.

Beck *et al.* recently utilized the venous pressure as a guide for pneumoperitoneum therapy.[8] When a considerable rise in venous pressure followed the induction of pneumoperitoneum, they advised that the procedure should be discontinued. This conclusion was based on the assumption that when the diaphragm does not function properly because of adhesions or atrophy, or when the lungs have almost completely lost their elasticity, the effect of the pressure transmitted by the pneumoperitoneum will be only passive. The lungs will then be compressed without increase in their ventilation. This phenomenon may lead to accumulation of blood in the right ventricle, decreased cardiac output, and prolongation of the circulation time. Further hypoxia and dyspnea may be precipitated, and eventually cardiac failure. A good indication of the effectiveness of pneumoperitoneum is manifested by a drop in, or lack of significant change in, the venous pressure.[8]

The interrelationships for normal individuals between the pressure in the peritoneal cavity, pleural cavity, trachea, and peripheral veins are described in Fig. 26A.

The intra-abdominal pressure near the umbilicus is essentially zero (atmospheric) because the abdominal walls are flexible and thus the atmospheric pressure is transmitted through them without alteration. In the immediate subdiaphragmatic region this pressure becomes slightly "negative" (less than atmospheric) and follows the changes in the intrapleural pressure.[9] The intrapleural pressure is always negative, about -2 cm of H_2O pressure in expiration and -6 to -8 cm of H_2O pressure in inspiration; this negativity, exerted upon the upper surface of the diaphragm in expiration, pulls the diaphragm into its normal elevated position. The intratracheal pressure varies only slightly with respiration, ranging from -2 to $+1$ cm H_2O in the inspiratory and expiratory phases, respectively. The venous pressure is usually $+5$ to $+15$ cm of H_2O in inspiration, exhibiting a moderate increase in expiration. This venous pressure tends to vary directly with the intrapleural pressure.

The findings in an emphysematous patient are described in Fig. 26B. With progressive hyperinflation of the lungs and loss of elasticity, intratracheal and intrapleural pressure tends to become less negative. The decrease in the degree of intrapleural negativity is the important factor in explaining the descent of the diaphragm in these patients.[10]

peritoneum therapy in a patient with chronic pulmonary emphysema can be seen in Figs. 27 and 28



FIG 27 —S N (P A view) Chronic pulmonary emphysema showing increased radiance of lung fields, low position of the diaphragm and engorgement of hilar vessels Slight downward displacement of horizontal interlobar fissure (arrow)

III. Indications for Pneumoperitoneum Therapy

The indications for pneumoperitoneum therapy in chronic pulmonary emphysema are still the subject of considerable discussion The following concepts will serve as practical guides:

A The relative degree of reversible physiologic changes should be determined whenever possible by complete pulmonary function stud-

ies Some amount of pulmonary reserve must be present, before starting pneumoperitoneum



Fig 28 —S N (Same patient Fig 27) A therapeutic pneumoperitoneum has been instituted Note elevation of the horizontal interlobar fissure (arrow) and marked bilateral elevation of the diaphragm The points of reference are the intersection of the sixth anterior rib, diaphragmatic dome and the heart Note digitations of the muscular attachments of the diaphragm to the chest cage on the right

B There should be only an insignificant degree of active bronchial constriction Prior to instituting pneumoperitoneum therapy, maximum improvement should be effected with bronchodilator aerosols, alone or combined with intermittent positive pressure breathing, and infections should be cleared up with antibiotics

C Complete evaluation of the anatomical integrity of the dia-

phragm, relating to the presence of atrophic changes and adhesions, should be made by fluoroscopic and roentgenographic studies The simple sniff test and diaphragmatic exercise technique described in Chapter IV may be employed for such evaluation under fluoroscopic observation

D It should always be kept in mind *that the purpose of pneumo*peritoneum in chronic pulmonary emphysema is not to decrease lung movements as in pulmonary tuberculosis, but rather to improve *the efficiency of the diaphragm, thus enabling* better ventilation. Restoration or improvement of the dynamic function of the diaphragm is the main object. For these reasons smaller amounts of air are employed in pneumoperitoneum therapy for patients with chronic pulmonary emphysema than for those with pulmonary tuberculosis

E Individual refills will vary from several hundred to one thousand cc at weekly intervals When fluoroscopic control shows that the successful elevation of the diaphragm is also followed by adequate motion, refills should be given at *longer intervals, several weeks, for* example.

F When the more serious manifestations of chronic pulmonary emphysema, namely the carbon dioxide intoxication *syndrome with* respiratory acidosis, cannot be relieved by adequate intermittent positive pressure therapy with 40 per cent oxygen, or when adequate movements of the chest cage and diaphragm do not follow chamber respirator treatment, immediate pneumoperitoneum should be instituted *Two or more refills may be required in the first twenty-four* hours as an emergency procedure to correct the hypoventilation observed in these patients[30] One should not hesitate to *administer* large amounts of air, regardless of *further decrease in gross ventila*tion However, the alveolar ventilation will become more effective as a result of the striking reduction in residual volume.

G. Constitutional characteristics of the *patient are not of sufficient significance in* determining the indications for pneumoperitoneum. *We have observed beneficial results* in patients with *flat, thin ab*domens, considered by many physicians as poor risks for this type of therapy.

IV. Complications from Pneumoperitoneum Therapy

Patients may complain of abdominal or shoulder-top pain and constipation Unexplained fever may occasionally also be noted. The procedure is not entirely free from all risk, and more serious sequelae have been reported, such as bleeding into the peritoneal cavity, air embolization, perforation of a viscus, tearing of intraperitoneal adhesions, subcutaneous and mediastinal emphysema, pneumothorax and peripheral vascular collapse An occult hernia may become manifest following therapy, but if pneumoperitoneum is sufficiently warranted, a surgical herniorrhaphy should be performed. Twenty such cases, recently reported, were followed by excellent and uncomplicated results[157]

V. Complementary Measures to Pneumoperitoneum Therapy

The use of the following complementary measures is of the utmost importance:

A Breathing Exercises Pneumoperitoneum therapy should be considered as merely the first step toward the restoration of diaphragmatic function Continuous encouragement from the physician or physiotherapist is necessary, to educate and stimulate the patient in [illegible]

(S[illegible]

ter[illegible]

habilitation with other types of invalidism, particularly pol[illegible] or orthopedic ailments Our results have been most gratify[illegible] we have followed these concepts

B Belts and Binders Their use is primarily indicated in [illegible] emphysematous patient However, they should be designed [illegible] for this purpose. Their purpose is the maintenance of a rigid [illegible] wall, in order to project the intraperitoneal pressure [illegible] upward for a most effective action toward the diaphragm [illegible] different types are available, such as the Gordon, Kerr, [illegible] (See Chapter XIII)

C Intermittent Positive Pressure Breathing (1) [illegible]

patients in whom the disease is complicated by large giant cysts, or multiple bullae, have responded poorly to pneumoperitoneum treatment,[32] because the emptying of such sacs is very irregular, and in some patients postpneumoperitoneum rearrangements may block them even farther. In such cases, when palliative surgery is not feasible, the combination of intermittent positive pressure breathing in inspiration, IPPB/I, and pneumoperitoneum should be considered. Restoration of patent airways can lead to shrinkage of the cysts.

(2) Whenever patients under pneumoperitoneum treatment have a severe attack of bronchial constriction or an upper respiratory infection that threatens their already diminished pulmonary function, a course of IPPB/I with supplemental antibiotic and bronchodilator aerosols, should be instituted at once. (See Chapter VIII.)

CHAPTER XIII
Breathing Exercises

Re-establishment of the normal mechanical pattern of respiration should be attempted after maximal relief from bronchoconstriction and bronchial infection has been attained by properly directed treatment Both active and passive diaphragmatic breathing exercises may reduce pulmonary overdistention in chronic pulmonary emphysema. Such exercises have long been advocated in England[4] They have also been discussed at some length by Livingstone[10]. The disease usually imposes certain pathologic changes that only a continuous program of physiotherapeutic rehabilitation can hope to improve, premature enthusiasm over early good results causes the patient and therapist to neglect the sustained efforts that are necessary for continued improvement Similar exercises are very valuable in the prevention of deformities in the chest of patients who have undergone thoracic surgical procedures

A thorough evaluation of the patient's breathing pattern, posture, and thoracic contour as well as of his degree of pulmonary function reserve must precede attempts at physical rehabilitation therapy

The chest is measured with a tape measure at three different thoracic levels: fourth rib, xiphoid process, and below the costal margin[110] Various chest areas are carefully observed in regard to their motility Most commonly one sees the typical emphysematous chest with an increased anteroposterior diameter, moving up and down with respiration as a rigid unit, without appreciable inspiratory expansion In other patients, the lower chest is held rigid while the upper chest is expanded through intensive strain by the accessory muscles The degree of spinal deformity should be determined The closely similar patterns in the pathogenesis of both chronic pulmonary emphysema and kyphoscoliotic heart and lung disease are well recognized today Correction of these deformities may lead to amelioration of the basic respiratory insufficiency as well as improvement in

the defective posture. The boost in the patient's morale provided by correction of the abnormal posture is of great psychologic importance

Functional reserve should be measured by complete pulmonary function studies and these determinations should be repeated at yearly intervals During therapy, weekly or monthly determinations of the maximal breathing capacity or timed vital capacity aid in evaluating the patient's progress.

In the normal individual, motion of the diaphragm contributes significantly to the movement of air in and out of the chest. Women utilize diaphragmatic breathing to a larger extent than men. It has been estimated that in the normal male, diaphragmatic breathing contributes at least 30 per cent of the vital capacity

Barach[19] has emphasized the importance of special training and daily practice for developing diaphragmatic breathing in patients with pulmonary emphysema He teaches the patient to lower the diaphragm during inspiration, and makes certain he has done so by watching for protrusion of the abdomen The patient is instructed to press with both hands below the umbilicus inward and upward *during the latter third of expiration.* These procedures tend to restore the lost diaphragmatic excursions. The expiratory phase may be carried out passively for the sick patient and may help in eliminating trapped air. During these exercises the lips may be kept pursed in expiration These exercises should be practiced lying down with the knees drawn up at first, one hand on the abdomen and one on the chest, the abdomen should be protruded forward during inspiration, with little or no chest movement After two minutes' *trial, the same exercise should be done sitting up* and then while walking This type of breathing should be encouraged at all times in order to develop it as an automatic pattern Many patients learn this procedure quickly whereas others, particularly patients with flat abdomens and erect bearing, have considerable difficulty with these same exercises At the beginning of treatment, the use of a head-down position, accomplished by elevating the foot of the bed or by the use of posture chairs or boards, may be an effective means of [illegible] breathing.[21]

[illegible] ng patterns can be effectively [illegible] ned to improve the spine and chest relationships as well as the function of the

diaphragm In addition, abdominal and skeletal supports (orthopedic braces) may be used

There are many types of abdominal supports (emphysema belts) intended to provide the abdominal compression necessary for elevating the diaphragm to the normal expiratory level They should be designed to direct pressure inward and upward and also to provide the necessary support for the abdominal wall The normal diaphragmatic arch may be restored by wearing a snug abdominal support, which should not be too tight and should be worn only during the day Some relief of respiratory symptoms may be noted in many patients Some use the Burgess-Gordon two-band belt, and others use the Camp emphysema belt with inflatable pressure pad or similar apparatus

We have found a definite routine more helpful than the occasional use of these rehabilitation procedures The nose, throat, and upper respiratory passages should be emptied of all secretions before starting the exercises The patient is instructed to take from 3 to 6 inhalations of Vaponefrin or Isuprel upon arising and one hour before lunch, supper, and bedtime This is followed by the diaphragmatic breathing previously described After the patient has mastered this and carried it out for one or more weeks, a complimentary program of breathing reeducation should be instituted This is done by corrective breathing exercises Bending slightly forward, the patient starts with arms hanging down in front of the body and the backs of the hands together, he inspires slowly and quitely through the nose, raising arms over the head, then the palms are rotated outward and the arms are extended horizontally at the shoulders with the palms upward The patient gradually assumes the erect position during this maneuver The arc is reversed in expiration, leading slowly back to the starting position Expiration should be prolonged and through the mouth, with the lips pursed making an F or S sound The exercises should not be forceful After these breathing exercises, the diaphragmatic breathing exercises previously mastered are then performed The latter are most important for they encourage mobility of the diaphragm and lower part of the chest, thus effecting more efficient emptying of the lungs Both exercises should be repeated from six to twelve times, depending upon the capabilities of the patient Training is encouraged, but fatigue should be avoided The exercises are finished in time to permit a rest period of from

fifteen to thirty minutes before each meal. The effect on the patient should be observed lest treatment do more harm than good

A skilled and interested physiatrist may be helpful in the application of more extensive breathing and muscle group exercises.[4] Gentle *upper abdominal massage in expiration and the use of vibratory* apparatus on the chest may help make the patient more comfortable In cooperative patients the results are worth the effort. The physiatrist can eventually develop the program on a more varied and broader basis, attempting at all times to regain the balanced use of the respiratory muscles According to May,[110] the aims of physiotherapy should be the following:

(a) Achievement of relaxation by means of rhythmic swinging and stretch-relax exercises especially directed to the accessory muscles and shoulder girdle

(b) To retrain normal breathing habits. This is directed especially to the diaphragm and lower chest.

(c) To correct abnormal posture by means of correct chest and trunk mobilization, balance, and walking exercises

The combined efforts of physician, physiatrist, and cooperative *patient may yield striking results The improvement noted by fluoros*copy and confirmed by pulmonary function studies should be called to the patient's attention and will serve to encourage him to continued efforts

There has been some suggestive evidence that *electrophrenic respiration* may be helpful in reeducating the diaphragm to proper function in the patient with chronic pulmonary emphysema [111] The possibilities of this procedure in selected patients, at the onset of the breathing rehabilitation program, are worth further investigation

Appendix: Methodology*

I. The Spirographic Tracing

A *The tidal volume, expiratory reserve volume, inspiratory capacity and vital capacity* are lung volumes which are determined with a spirometer which produces a permanent kymographic record, the spirogram. We employ a modified Benedict-Roth spirometer with a bell of 9 liters capacity and soda-lime carbon dioxide absorber[83]

In our laboratory, the spirogram is obtained with the patient in the sitting position. Graphic recordings of quiet respiration are made, with the patient first breathing room air (Fig 29a_1) and shortly thereafter oxygen (Fig 29a_2) Each inspiration or expiration represents the *Tidal Volume* After several minutes of such respiration the *Resting Minute Ventilation* is obtained The patient is then instructed at the end of a normal expiration to inhale as deeply as he can, to provide a measure of the *Inspiratory Capacity* (Fig 29c)

* Physicians interested in cardiopulmonary function studies should refer to the texts by Cournand,[44] Comroe,[31] Consolazio *et al*,[49] and the papers by Baldwin *et al*[8, 1, 4, 5]

Following another interval of quiet breathing, at the end of a normal expiration, the patient is again instructed to breathe out as hard and as long as he possibly can, to record the *Expiratory Reserve Volume* (Fig 29b) The *Vital Capacity* measurement (Fig 29d) is obtained by

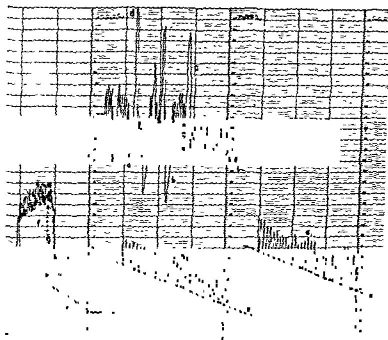


Fig 29—Spirogram in a patient with chronic pulmonary emphysema a_1 Tidal volume and resting minute ventilation with air a_2 Resting minute ventilation with [illegible]
ity *d* Vital cap[illegible]
g Trapping of [illegible]
right to left The time interval between two vertical lines of the graph paper is one minute, except for the recording of the M B C —when the drum rotates at a greater speed—where the time interval is 12 seconds

exhorting the patient to take as deep a breath as possible and then to breathe out as hard and as long as he can.

When respiratory tracings are recorded with the soda-lime carbon dioxide absorber in place, the slope of the base line (resting ventila-

tion) represents the oxygen consump[illegible] metabolism determinations There are [illegible] to obtain spirograms demonstrating the [illegible] inspired room air as compared to the [illegible] pure oxygen is breathed All gas volumes are [illegible] temperature, standard pressure and saturation [illegible] (BTPS)

Although the *tidal volume* varies greatly [illegible] average value is usually given as 500 cc. The [illegible] more among normal individuals, so that an [illegible] liters, for example, will not indicate whether [illegible] abnormal Vital capacity readings should be [illegible] of various formulae, which take into consideration [illegible] age, height and weight[188].

Males

1) 2 5 L/M² Body Surface
2) 25 ml /cm Height
3) [27 63 − (0 112 × Age)] × Height in cm

Females

1) 2 0 L/M² [illegible]
2) 20 ml /cm [illegible]
3) [21 78 − [illegible]] in cm [illegible]

It must be understood that the range of vital [illegible] individuals may vary as much as 20 per cent [illegible] normal values

The vital capacity can also be evaluated on the [illegible] the total lung capacity Hurtado *et al*[illegible] gave [illegible] per cent or greater, Greifenstein *et al*[illegible] studied [illegible] the age of 50 years, and found an average ratio [illegible]

In our studies, by employing Baldwin's pred[illegible] mula # 3) we obtained in ten normal subjects an [illegible] of 116 per cent of the predicted normal

The *expiratory reserve volume* may vary in the [illegible] day to day by as much as 8 per cent, varying [illegible] from the mean value in normal individuals The [illegible] volume is also greatly influenced by the position [illegible] examination A decrease of as much as 800 cc [illegible] when the patient changes from the standing to [illegible] The normal expiratory reserve volume constit[illegible] per cent of the vital capacity with the *inspirator*[illegible]

for the remaining 75 to 80 per cent With advancing years it appears that the expiratory reserve volume tends to increase at the expense of the inspiratory capacity[75], that is, the mid-position tends to rise with aging in the normal individual

Timed Vital Capacity In addition to determining the absolute value of the vital capacity, investigators have frequently measured its relationship to the time factor Gross measured the time required for full maximum expiration in pulmonary and cardiac diseases[77] He divided the vital capacity by the expiratory time and called this the "expiratory velocity" Gaensler simplified the study of vital capacity-time relationships by attaching a timing device to the spirometer (Vitalometer*), indicating the volume exhaled during the first one, two or three seconds of the vital capacity[88]

In our laboratory we have devised a transparent ruler for time-vital capacity relationships, which can be used in conjunction with the spirographic record obtained from the spirometer[118] The volume of air exhaled during any desired time interval of the vital capacity curve can be computed very easily, by simply placing the ruler A over the spirographic tracing B (Fig 30)

The distance between two vertical lines of the ruler corresponds to one second of the recording time on the spirograph when it is turning at high speed On the ventilograph paper the distance between two vertical lines is 12 seconds One millimeter vertical excursion of the recording needle equals 20.73 cubic centimeters The ventilograph paper is lined with horizontal lines placed at two-millimeter intervals Thus, to measure the *volume* for any one-second interval, the height of the tracing is measured in millimeters, multiplied by 20 73, and then corrected for BTPS

B Ventilation studies, such as *minute ventilation* and *maximal breathing capacity*, can be determined readily with the spirometer

Tidal volume, multiplied by the respiratory rate per minute, yields the minute ventilation This can also be measured by having the patient breathe directly through a two-way valve connected to a gasometer Resting ventilation is expressed as liters per minute per square meter of body surface area The average normal value is 3 6 L /M² for males and 3 2 L /M² for females[13] Normal subjects

* Manufactured by Warren E Collins, Inc , Boston, Mass

over 50 years of age were found to have a minute ventilation of 6.1 L./M.[2] for males and 5.4 L./M.[2] for females.[75]

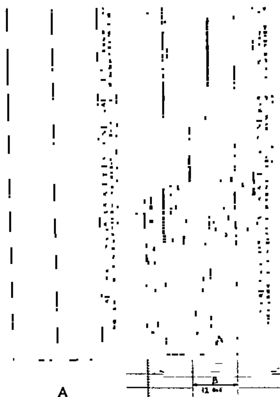


FIG. 30. Transparent ruler for determining time-vital capacity relationships.

However, the total minute ventilation is not as important as the *effective* ventilation. Not all of the inspired air reaches the lungs with each inspiration. As the patient breathes in, the air in the trachea and bronchi descends to the alveoli *first*. On expiration, the last portion of the expired air remains in the trachea and bronchi, and it is

for the remaining 75 to 80 per cent. With advancing years it appears that the expiratory reserve volume tends to increase at the expense of the inspiratory capacity[75]; that is, the mid-position tends to rise with aging in the normal individual.

Timed Vital Capacity In addition to determining the absolute value of the vital capacity, investigators have frequently measured its relationship to the time factor. Gross measured the time required for full maximum expiration in pulmonary and cardiac diseases.[77] He divided the vital capacity by the expiratory time and called this the "expiratory velocity" Gaensler simplified the study of vital capacity-time relationships by attaching a timing device to the spirometer (Vitalometer*), indicating the volume exhaled during the first one, two or three seconds of the vital capacity.[88]

In our laboratory we have devised a transparent ruler for time-vital capacity relationships, which can be used in conjunction with the spirographic record obtained from the spirometer.[115] The volume of air exhaled during any desired time interval of the vital capacity curve can be computed very easily, by simply placing the ruler A over the spirographic tracing B (Fig. 30)

The distance between two vertical lines of the ruler corresponds to one second of the recording time on the spirograph when it is turning at high speed On the ventilograph paper the distance between two vertical lines is 12 seconds. One millimeter vertical excursion of the recording needle equals 20.73 cubic centimeters The ventilograph paper is lined with horizontal lines placed at two-millimeter intervals Thus, to measure the *volume* for any one-second interval, the height of the tracing is measured in millimeters, multiplied by 20.73, and then corrected for BTPS.

B. Ventilation studies, such as *minute ventilation* and *maximal breathing capacity*, can be determined readily with the spirometer. Tidal volume, multiplied by the respiratory rate per minute, yields the minute ventilation. This can also be measured by having the patient breathe directly through a two-way valve connected to a gasometer. Resting ventilation is expressed as liters per minute per square meter of body surface area. The average normal value is 3.6 L./M.[2] for males and 3.2 L./M.[2] for females.[33] Normal subjects

* Manufactured by Warren E. Collins, Inc., Boston, Mass

over 50 years of age were found to have a minute ventilation of 6.1 L./M.² for males and 5.4 L./M.² for females.[75]

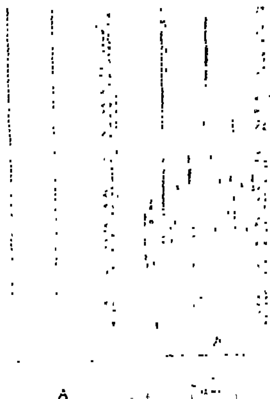


FIG. 30.—Transparent ruler for determining time-vital capacity relationships.

However, the total minute ventilation is not as important as the *effective* ventilation. Not all of the inspired air reaches the lungs with each inspiration. As the patient breathes in, the air in the trachea and bronchi descends to the alveoli *first*. On expiration, the last portion of the expired air remains in the trachea and bronchi, and it is

this expired air which is re-inspired at the beginning of the next breath This "respiratory dead space" amounts to about 150 cc.

For example, in two patients, who are both hyperventilating at 7 liters per minute, assume that patient *A* has a tidal volume of 500 cc. and a respiratory rate of 14 per minute, while patient *B* has a tidal volume of 280 cc and a respiratory rate of 25 per minute The effective minute ventilation of patient *A* is 14 × (500 − 150) or 4900 cc., and of patient *B* is 25 × (280 − 150) cc. or 2250 cc., less than half that of patient *A* It must be realized that pulmonary gas exchange may be abnormal in the presence of normal minute ventilation and even in the presence of normal alveolar ventilation, depending on ventilation-perfusion relationships and diffusion factors (see Chapter III)

The Maximal Breathing Capacity (*M.B.C*) can be recorded on a spirometer equipped with a Reichert integrating counter, ratchet and pawl device, by means of which a second writing pen is activated during inspiration only, so that it records a continually rising line[128] By means of a reducing gear, the motion of this pen is held to 1/25 that of the regular recording pen. The vertical distance traveled by this pen in any interval of time represents the sum of all inspirations during that interval, by this means the ventilatory volume per unit is thus determined directly. The graphs obtained in this way are demonstrated in Fig 20f During the determination of M B.C., all possible sources of resistance to air flow must be removed. For this reason the soda-lime canister is taken out. The rubber tubing should be short, and at least one inch in diameter.

A simpler yet effective method of determining the M.B C. is to collect the expired air in a compensated Tissot spirometer or a Douglas collecting bag The patient should breathe through a high-velocity, low-resistance valve of the Rudolph type which is connected by a two-inch rubber tubing to the reservoirs. When the Douglas bag is used the volume of air is measured with a gas meter The M.B C determination may be performed during a period of 12, 15, 20, or 30 seconds, the result is expressed in liters per minute *The subject is encouraged to breathe as hard and fast as he can* This test, perhaps more than any other, depends on the co-operation and willingness of the subject to exert himself to the utmost

The maximal breathing capacity varies greatly between normal

individuals, as do all of the other pulmonary function tests In order to evaluate the determined maximal breathing capacity, the results must be compared with predicted values [8, 74, 75] We use the prediction formulae of Baldwin[1]·

✓ In males· 86.5 − (0 522 × Age in years) × M² B S
In females 71 3 − (0 474 × Age in years) × M² B S

Gray *et al* [74] found no relationship between the M B C and age, height, and weight, and only slight relationship to body surface area These investigators measured the maximal breathing capacity in a large number of healthy young individuals and found the following normal values 167 1 liters/minute ± 13 per cent for males and 115 8 liters/minute ± 18 per cent for females In these studies the maximal breathing capacity determination was carried out for 20 seconds Greifenstein *et al* [76] found that the maximal breathing capacity in normal adults past the age of 50 years was 68.8 liters/minute (standard deviation ±27 8) for females, and 76 6 liters/minute (standard deviation ±25 0) for males

Besides these quantitative measurements, other information of value can be obtained from the analysis of the spirogram. Such matters as regularity or irregularity of the respiratory curves, the slope and duration of the inspiratory and expiratory curves of the vital capacity determination, the shift in mid-position or air trapping, will be obvious or readily determinable from these tracings (Fig 29g) "Trapping" refers to the failure of the lung to return to the same initial level of expiration when successive vital capacity performance tests are recorded or when the breathing is rapid and forceful

II. Determinations with the Open-Circuit Oxygen Dilution Method

A The Residual Volume of the lungs must be measured by indirect methods The closed-circuit method of Christie[33] described in 1932 has been largely superceded by the open-circuit methods of Darling *et al* [45] and Cournand *et al* [42] Recently, however, the closed-circuit method has been used again, employing helium [101] The open-circuit method is based on the elimination of gaseous nitrogen from the

lungs and body tissues, while 100 per cent oxygen is breathed At the end of 7 minutes of breathing 100 per cent oxygen, an alveolar sample is obtained and its nitrogen content is calculated.[135] First the *functional residual capacity* of the lungs is estimated by means of formulae. The residual volume is then obtained, by subtracting the expiratory reserve volume from the functional residual capacity The residual volume plus the vital capacity equal the *total lung capacity*

Either a Tissot spirometer or large Douglas bag may be used to collect the expired gases for determination of the functional residual capacity We use a Douglas bag The functional residual capacity is calculated according to the following formula[91]:

$$\text{F.R.C. (dry)} = \frac{[(V + d\,s.)(b - a)] - C}{\text{Alv. N}\,\bar{a} - \text{Alv. N}\,\bar{p}}$$

V	= volume in cc of air collected into Douglas bag or spirometer corrected to dry gas, at standard temperature and barometric pressure
$d\,s$	= dead space volume in cc. in the connecting system.
b	= per cent N_2 in spirometer or Douglas bag
a	= per cent N_2 in oxygen from tank.
$Alv\ N\,\bar{a}$	= per cent N_2 in alveolar air before the beginning of the determination
$Alv\ N\,\bar{p}$	= per cent of N_2 in alveolar air at end of oxygen breathing
C	= correction for N_2 excreted from the body during the 7 minutes when oxygen is breathed.

$$C \text{ in cc} = (B\,S/M^2 \times 96\,5) + 35$$

The dry F.R C. is next corrected for water vapor saturation, comparable to its state within the lungs:

$$\text{F R C. wet} = \text{F R C dry} \times \frac{\text{Barom. Pres. in mm. Hg}}{\text{Barom Pres in mm Hg} - 48}$$

The residual volume varies in normal subjects from day to day by as much as 5 5 per cent[126] Normal subjects over the age of 50 years were found to have an average functional residual capacity of 3400 cc , and a residual volume of 2430 cc[75]

The evaluation of the total lung capacity necessitates some method of predicting the normal total lung capacity for that particular

dividual However, Fowler[64] stated that the normal total lung capacity cannot be predicted with an accuracy of greater than ±15 to 20 per cent Bateman recently stated that the best correlation of the total lung capacity is in connection with body height [23] The most common formula for predicting total lung capacity is based on the ratio of vital capacity to total lung capacity, which varies with age The formula is $\frac{\text{Vital Capacity}}{A}$ where A = 80 for the ages of 16–34 years, 76 6 for 35–49 years, and 69 2 for 50–69 years However, this formula can be applied to normal individuals only In pulmonary disease the vital capacity varies greatly, and is usually low

Calculating the total lung capacity with the vital capacity actually obtained may yield abnormally low, so-called "normal" predicted total lung capacities which, moreover, may vary tremendously from one time to another For this reason, other investigators have used the predicted vital capacity to calculate the predicted total lung capacity [174] We have previously pointed out that the current prediction formulae for vital capacity often yield small vital capacities in normal subjects Hence the use of the predicted vital capacity yields a predicted total lung capacity which frequently is too small [83]

In order to eliminate both of the above objections in calculating the predicted total lung capacity, we have used the largest vital capacity actually obtained in the patient, either before or after treatment [83] If this vital capacity, even after treatment, is less than the vital capacity value calculated with the prediction formula, the predicted vital capacity is used in computing the predicted total lung capacity is developed ... of predicted total lung capacity ... advisable to compare several ...ally

calculated values, ...

The ratio of the residual volume to the ... According to Baldwin this ratio computed as follows $\frac{R\,V}{T\,L\,C} \times 100$ According to Baldwin this ratio averaged 20 0 per cent for ages 16–34 years, 23 4 per cent for ages 35–49 years, and 30 8 per cent for ages 50–69 years [6] This study considered a ratio greater than 35 per cent as definitely indicative of emphysema In normal subjects over 50 years of age the ratio was found to be 40 9 per cent [75]

B In addition to these static volumes (F R C , R V , and T L C),

lungs and body tissues, while 100 per cent oxygen is breathed. At the end of 7 minutes of breathing 100 per cent oxygen, an alveolar sample is obtained and its nitrogen content is calculated.[135] First the *functional residual capacity* of the lungs is estimated by means of formulae. The residual volume is then obtained, by subtracting the expiratory reserve volume from the functional residual capacity. The residual volume plus the vital capacity equal the *total lung capacity*.

Either a Tissot spirometer or large Douglas bag may be used to collect the expired gases for determination of the functional residual capacity. We use a Douglas bag. The functional residual capacity is calculated according to the following formula[6]:

$$\text{F.R.C. (dry)} = \frac{[(V + \text{d.s.})(b - a)] - C}{\text{Alv. N } \bar{a} - \text{Alv. N } \bar{p}}$$

V = volume in cc. of air collected into Douglas bag or spirometer corrected to dry gas, at standard temperature and barometric pressure.

d.s. = dead space volume in cc. in the connecting system

b = per cent N_2 in spirometer or Douglas bag.

a = per cent N_2 in oxygen from tank.

Alv. N $\bar{a}$ = per cent N_2 in alveolar air before the beginning of the determination

Alv. N $\bar{p}$ = per cent of N_2 in alveolar air at end of oxygen breathing

C = correction for N_2 excreted from the body during the 7 minutes when oxygen is breathed

$$C \text{ in cc} = (\text{B.S./M.}^2 \times 96.5) + 35.$$

The dry F.R C. is next corrected for water vapor saturation, comparable to its state within the lungs:

$$\text{F R C wet} = \text{F R C. dry} \times \frac{\text{Barom. Pres in mm Hg}}{\text{Barom. Pres. in mm Hg} - 48}$$

The residual volume varies in normal subjects from day to day by as much as 5.5 per cent.[116] Normal subjects over the age of 50 years were found to have an average functional residual capacity of 3400 cc , and a residual volume of 2130 cc.[75]

The evaluation of the total lung capacity necessitates some method of predicting the normal total lung capacity for that particular

individual However, Fowler[64] stated that the normal total lung capacity cannot be predicted with an accuracy of greater than ±15 to 20 per cent Bateman recently stated that the best correlation of the total lung capacity is in connection with body height[23] The most common formula for predicting total lung capacity is based on the ratio of vital capacity to total lung capacity, which varies with age The formula is $\frac{\text{Vital Capacity}}{A}$ where A = 80 for the ages of 16–34 years, 76 6 for 35–49 years, and 69 2 for 50–69 years However, this formula can be applied to normal individuals only In pulmonary disease the vital capacity varies greatly, and is usually low

Calculating the total lung capacity with the vital capacity actually obtained may yield abnormally low, so-called "normal" predicted total lung capacities which, moreover, may vary tremendously from one time to another For this reason, other investigators have used the predicted vital capacity to calculate the predicted total lung capacity.[174] We have previously pointed out that the current prediction formulae for vital capacity often yield small vital capacities in normal subjects Hence the use of the predicted vital capacity yields a predicted total lung capacity which frequently is too small[83]

In order to eliminate both of the above objections in calculating the predicted total lung capacity, we have used the largest vital capacity actually obtained in the patient, either before or after treatment[87] If this vital capacity, even after treatment, is less than the vital capacity value calculated with the prediction formula, the predicted vital capacity is used in computing the predicted total lung capacity Until a better formula of predicted total lung capacity is developed for patients with pulmonary disease, it is advisable to compare several

computed as follows. $\frac{\text{R V}}{\text{T L C}} \times 100$ According to Baldwin this ratio averaged 20 0 per cent for ages 16–34 years, 23 4 per cent for ages 35–49 years, and 30 8 per cent for ages 50–69 years.[6] This study considered a ratio greater than 35 per cent as definitely indicative of emphysema In normal subjects over 50 years of age the ratio was found to be 40 9 per cent[75]

B In addition to these static volumes (F R C., R V , and T L C),

the open-circuit method also yields the "*Index of Intrapulmonary Mixing*," which is the per cent of nitrogen left in the lungs after the breathing of 100 per cent oxygen for seven minutes.

The method of Darling *et al*, measuring the alveolar nitrogen after the breathing of 100 per cent oxygen for seven minutes, is *a measure of air distribution into the lungs*.[47, 48] They considered 2.5 per cent of nitrogen left at the end of the test as the upper limit of normal. Motley believes, however, that when the alveolar sample is obtained close to the mouth, 1.5 per cent should be considered as the normal limit.[118] The percentage of alveolar nitrogen, the index of intrapulmonary mixing, expresses the degree of removal of nitrogen from the alveolar air by pure oxygen breathing.

Nonetheless, since the *rate* of nitrogen removal depends on such factors as the functional residual capacity, the effective tidal volume, the respiratory rate and intrapulmonary distribution factors, it is possible by hyperventilation to obtain a normal index at the end of seven minutes, although one of these factors may be abnormal. When the nitrogen elimination is followed by the use of a continuous electronic nitrogen analyzer,[174] a method which takes these variable factors into consideration, unevenness of aeration will be noted, although the index at the end of seven minutes may be normal.

III. Miscellaneous Ventilation Studies

A. The Breathing Reserve is the difference between the minute ventilation and the maximal breathing capacity, and is expressed in L./min. The breathing reserve is also expressed in percentage of the maximal breathing capacity by the formula:

$$\frac{\text{M.B.C.} - \text{minute ventilation}}{\text{M.B.C.}} \times 100.$$

The breathing reserve is greater than 95 per cent at rest, and is more than 80 per cent after exercise in normal subjects.

B. The Ventilation Equivalent is the number of liters of air that are ventilated for each 100 cc. of oxygen consumed. The normal values for ventilation equivalent range between 2.2 and 2.5 liters. This equivalent is normal in metabolic hyperpnea, but is increased in the compensatory hyperventilation of certain pulmonary diseases.

C. The Air Velocity Index (*A V I*) is the ratio of the percentage of the predicted M B C over the percentage of the predicted vital capacity [67]

$$A.V.I. = \frac{\% \text{ of predicted M B C.}}{\% \text{ of predicted V C}}$$

The normal index is 1 0. This index will indicate whether there is more obstruction to air flow (*obstructive insufficiency*) than there is *loss of functioning lung tissue* (*restrictive insufficiency*), *or vice versa*

D Instantaneous Air Flow Measurements The development of the pneumotachograph has opened many new avenues in the study of pulmonary ventilation [97] At first this was an instrument which measured the instantaneous rate of air flow during inspiration, subsequently an instrument was designed to study expiratory air flow.[147] The instrument has undergone further changes and improvements, to record instantaneous response in both inspiration and expiration with minimal lag and inertia, and without significant resistance to air flow Detailed studies have been reported with such an apparatus, on air flow and factors governing air flow.[123 124 148]

IV. Bronchospirometry

The technique of bronchospirometry has been reviewed in detail [69 70] In principle, it consists of passing a double lumen catheter into the trachea and into the left bronchus just past the carina The opening to one lumen is at the tip of the catheter, protruding into the left bronchus; a rubber cuff, located proximal to this opening, is inflated, closing off the left bronchial tree Another opening leading to the second lumen of the catheter is located a few inches higher (above the carina), and connects with the right bronchial tree A rubber cuff located proximal to this opening is inflated, closing off the right lung from its connection with the other lung and with the trachea Thus a separate passage is established for each lung

Lung volumes, ventilation and gas exchange of each lung can now be studied separately Twin spirometers of the Benedict-Roth type may be used for the spirographic studies The normal right lung contributes 55 to 65 per cent of the total lung performance [4]

There are several contra-indications to bronchospirometry, mainly

tracheobronchial tuberculosis with ulcerations, recent hemoptysis (within two weeks), obstruction of the left main bronchus preventing proper placement of the catheter, and far advanced tuberculosis with severe symptoms and toxicity.[70]

V. Arterial Blood Studies

The arterial blood is usually examined for oxygen content, capacity, saturation, and tension[129, 132, 143], buffer base[141]; and pH. The average normal values are presented in Table 8

TABLE 8—*Normal Values for Oxygen, Carbon Dioxide, pH, and Buffer Base in the Arterial Blood*

	Baldwin[4]		Singer and Hastings[148]		Greifenstein[78]	
	Mean	S D	Mean	S D.	Mean	S D
O_2 saturation (%)	96.2	(1.2)	97.4	(2.1)	96.4	(1.6)
pO_2 (mm. Hg)	—	—	97.1	(2.5)	—	—
CO_2 content, whole blood						
mM/L	—	—	22.2	(0.9)	21.84	(2.1)
Vol %	52.0	(2.4)	49.5	(2.0)	—	—
pCO_2 (mm. Hg)	43.7	(3.5)	41.6	(2.9)	38.6	(4.7)
pH	7.43	(0.02)	7.39	(0.03)	7.42	(0.03)
Buffer Base (mEq/L)	—	—	45-55		—	—

The blood sample should be obtained anaerobically through a Cournand indwelling needle placed in the brachial or radial artery. The determinations are made on the blood obtained at rest and after standard exercise, which usually consists of 30 steps per minute up and down a platform 20 cm high or on a treadmill.

Fig. 31 illustrates the set-up for arterial blood sampling. Part B, the insert needle, fits inside part C, protruding slightly beyond the tip of C with its sharp beveled needle point. The needle is introduced into the artery in this way: when the blood begins to flow through B, this part is then withdrawn from C, allowing the blood to flow rapidly and freely through C. When the needle is to be left in the artery between sampling, the closed stylet A replaces B.

VI. Cardiac Catheterization

The catheter is introduced through the median basilic vein in the forearm until it reaches the right heart and pulmonary artery.[45]

Mixed venous blood samples are thus obtained, as well as pressure readings on a manometer Simultaneously with the venous samples, arterial blood is drawn through an indwelling needle in one of the peripheral arteries, and expired air is collected and measured in a spirometer or Douglas bag

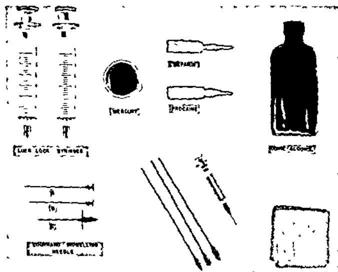


FIG 31 —Tray for arterial blood sampling.

The mixed venous blood and arterial blood are analyzed for oxygen intake and CO_2 output per minute These results are applied to the Fick equation in calculating the *cardiac output* (C O)

$$\text{C O (L./min)} = \frac{O_2 \text{ intake (cc/min.)}}{O_2 \text{ arterial} - \text{venous difference (cc/L blood)}}$$

or

$$= \frac{CO_2 \text{ output (cc/min)}}{CO_2 \text{ arterial} - \text{venous difference (cc/L blood)}}$$

$$\text{Cardiac index} = \frac{\text{C O.}}{\text{B S /M}^2}$$

$$\text{Stroke volume} = \frac{\text{C O}}{\text{Pulse rate}}$$

As the tip of the catheter is passed through the right auricle, right ventricle, and pulmonary artery, the pressure readings are obtained. The level of pressure and the characteristics of the blood pressure curves in the auricles, ventricles and large vessels are quite distinct. *Table 9* lists the significant data obtained through cardiac catheterization.

TABLE 9.—*Normal Values for Cardiac Output and Pulmonary Artery Pressures*

Cardiac Output (L./min.)	5-6	
Cardiac Index (L./min./M²)	3.6-4.5	
Stroke Volume (cc.)	70-80	
Pulmonary Artery Pressure (mm. Hg)		
Systolic		25
Diastolic		9
Mean		15
Pulmonary "capillary" Pressure (mm. Hg)		9
Pulmonary Resistance (dynes/sec./cm.,⁻⁵)		250

Pulmonary arteriolar resistance is calculated from simultaneous determinations of the cardiac output, pulmonary artery pressure and pulmonary "capillary" pressures with the formula[170]:

$$R = \frac{PA - PC}{CO} \times 1332$$

Where R = arteriolar resistance in dynes sec.$^{-5}$

PA = mean pulmonary artery pressure in mm. Hg

PC = *mean pulmonary "capillary" pressure in mm. Hg*

C.O. = cardiac output in cc. per second

1332 = *conversion factor from mm. Hg to dynes per cm.²*

Bibliography

[1] ALEXANDER, R S Influence of the Diaphragm Upon Portal Blood Flow and Venous Return Am J Physiol , *167* 738, 1951

[2] ALTSCHULE, M D Physiology in Diseases of the Heart and Lungs Cambridge, Harvard University Press, 1948

[3] ANDREWS, A H *Manual of Oxygen Therapy Techniques, Including Carbon Dioxide, Helium, and Water Vapor* Chicago, The Year Book Publishers, 1943

[4] ASTHMA RESEARCH COUNCIL Physical Exercises for Asthma, Eighth Edition London, Kings College, 1949

[5] AUSTRIAN, R , MCCLEMENT, J H , RENZETTI, A D , JR , DONALD, K W , RILEY, R L AND COURNAND, A Clinical and Physiological Features of Some Types of Pulmonary Diseases with Impairment of Alveolar Capillary Diffusion The Syndrome of "Alveolar Capillary Block " Am J Med , *11* 667, 1951

[6] BALDWIN, E DEF , COURNAND, A AND RICHARDS, D W , JR Pulmonary Insufficiency I Physiological Classification, Clinical Methods of Analysis, Standard Values in Normal Subjects Medicine, *27* 243, 1948

[7] BALDWIN, E DEF , COURNAND, A , AND RICHARDS, D W , JR Pulmonary Insufficiency II A Study of Thirty nine Cases of Pulmonary Fibrosis Medicine, *28* 1, 1949

[8] BALDWIN, E DEF , COURNAND, A AND RICHARDS, D W , JR Pulmonary Insufficiency III A Study of 122 Cases of Chronic Pulmonary Emphysema. Medicine, *28* 201, 1949

[9] BALDWIN, E DEF , HARDEN, K A , GREENE, D G , COURNAND, A AND RICHARDS, D W , JR Pulmonary Insufficiency IV A Study of 16 Cases of Large Pulmonary Air Cysts or Bullae Medicine, *29* 169, 1950

[10] BANYAI, A Pneumoperitoneum Treatment St Louis, C V Mosby, 1946

[11] BARACH, A L Physiological Methods in Diagnosis and Treatment of Asthma and Emphysema Ann Int Med , *12* 454, 1938

[12] BARACH, A L , MARTIN, J AND ECKMAN, M *Positive Pressure Respiration and its application to the Treatment of Acute Pulmonary Edema* Ann Int Med , *12* 754, 1938

[13] BARACH, A L AND SWENSON, P Effect of Breathing Gases under Positive Pressure on Lumens of Small and Medium-sized Bronchi Arch Int Med , *63* 946, 1939

[14] BARACH, A L AND MOLOMUT, N An Oxygen Mask Metered for Positive Pressure Ann Int Med , *17* 820, 1942

[15] BARACH, A L, GARTHWAITE, B AND RULE, C · Use of Penicillin Aerosol in Bronchopulmonary and Sinus Infections New York State J. Med, 46 1703, 1946
[16] BARACH, A L, GARTHWAITE, B, RULE, C, TALBOT, T R, JR, KERVAN, J D, BABCOCK, J AND BROWN, G · Penicillin Aerosol and Negative Pressure in Treatment of Sinusitis Am J Med, 1 268, 1946
[17] BARACH, A L Physiologic Therapy in Respiratory Diseases, Second Edition Philadelphia, J B Lippincott Co, 1948
[18] BARACH, A L Treatment of Anoxia in Clinical Medicine Bull New York Acad Med, 26 370, 1950
[19] BARACH, A L, BICKERMAN, H A AND BECK, G Advances in the Treatment of Non-Tuberculous Pulmonary Disease Bull New York Acad Med, 28 353, 1952
[20] BARACH, A L, BECK, G J, BICKERMAN, H A, AND SEANOR, E H Physical Methods Simulating Mechanisms of the Human Cough J Applied Physiol, 5 85, 1952
[21] BARACH, A L Personal Communication
[22] BARCROFT, J The [illegible]
High Altitude
[23] BATEMAN, J B [illegible] Capacities and Intra-pulmonary Mixing Normal Lung Capacities J Applied Phys [illegible]
[24] BECK G [illegible]

[25] B[illegible], JR Investigations Concerned with Problems of High Altitude Flying and Deep Diving; Application of Certain Findings Pertaining to Physical Fitness to the General Military Service Mil Surgeon, 90 9, 1942
[26] BEST, C H AND TAYLOR, H B The Physiological Basis of Medical Practice, fifth Edition Baltimore, Williams & Wilkins Co, 1950
[27] BJURSTEDT, A G H Interaction of Centrogenic and Chemoreflex Control of Breathing During Oxygen Deficiency at Rest Acta Physiol Scandinav, 12 1, 1946
[28] BONNER, C D [illegible]
Clinical Observ[illegible]
tients with Car[illegible]
Adrenocorticotr[illegible]
1952
[29] BOOTHBY, W M, MAYO, C W AND LOVELACE, W R, JR One Hundred Per Cent Oxygen, Indications for Its Use and Methods of Administration J A M A, 113 477, 1939
[30] CALLAWAY, J J AND MCKUSICK, V A Carbon Dioxide Intoxication in Emphysema, Emergency Treatment by Artificial Pneumoperitoneum New England J Med, 245 9, 1951
[31] CAMPBELL, J. M H AND POULTON, E P Oxygen and Carbon Dioxide Therapy New York and London, Oxford University Press, 1934

[32] CARTER, M G, GAENSLER, E A AND KYLLONEN, A Pneumoperitoneum in the Treatment of Pulmonary Emphysema New England J of Med, 243 549, 1950

[33] CHRISTIE, R V The Lung Volume and its Subdivisions I Methods of Measurement J Clin Investigation, 11 1099, 1932

[34] COMMITTEE ON PUBLIC HEALTH RELATIONS, N Y ACAD MED Standards of Effective Administration of Inhalational Therapy, Second Report J A M A, 144 25, 1950

[35] COMROE J H, JR, DRIPPS, R D, DUMKE, P R AND DEMING, M Oxygen Toxicity The Effect of Inhalation of High Concentrations of Oxygen for Twenty-four Hours on Normal Men at Sea Level and at Simulated Altitude of 18,000 Feet J A M A, 128 710, 1945

[36] COMROE, J H, JR, BAHNSON, E R AND COATES, E O, JR Mental Changes Occurring in Chronically Anoxemic Patients During Oxygen Therapy J A M A, 143 1044, 1950

[37] COMROE, J H, JR, ED-IN-CHIEF Methods in Medical Research, Vol 2 Chicago, Yearbook Publishers, Inc, 1950

[38] COMROE, J H, JR Interpretation of Commonly Used Pulmonary Function Tests Am J Med, 10 356, 1951

[39] COMROE, J H, JR Lecture at Boston City Hospital, June 3, 1952

[40] CONSOLAZIO, C F, JOHNSON, R E AND MARECK, E Metabolic Methods St Louis, C V Mosby Co, 1951

[41] COURNAND, A, RICHARDS, D W, JR AND DARLING, R C Graphic Tracings of Respiration in Study of Pulmonary Disease Am Rev Tuberc, 40 487, 1939

[42] COURNAND, A, BALDWIN, E DEF, DARLING, R C AND RICHARDS, D W, JR Studies on Intrapulmonary Mixing of Gases IV The Significance of the Pulmonary Emptying Rate and Simplified Open Circuit Measurement of Residual Air J Clin Investigation, 20 681, 1941

[43] COURNAND, A, YARMUSH, I G AND RILEY, R L Influence of Body Size on Gaseous Nitrogen Elimination During High Oxygen Breathing Proc Soc Exper Biol & Med, 48 280, 1941

[44] COURNAND, A, MOTLEY, H L, WERKO, L AND RICHARDS, D W, JR Physiological Studies of the Effects of Intermittent Positive Pressure Breathing on Cardiac Output in Man Am J Physiol, 152 162, 1948

[45] COURNAND, A, BALDWIN, J S AND HIMMELSTEIN, A Cardiac Catheterization in Congenital Heart Disease A Clinical and Physiological Study in Infants and Children N Y, Commonwealth Fund, 1949

[46] COURNAND, A Some Aspects of the Pulmonary Circulation in Normal Man and in Chronic Cardiopulmonary Diseases Circulation, 2 641, 1950

[47] DAMESHEK, W Personal Communication

[48] DARLING, R C, COURNAND, A, MANSFIELD, J S AND RICHARDS, D W, JR Studies on Intrapulmonary Mixture of Gases Nitrogen Elimination from Blood and Body Tissues During High Oxygen Breathing J Clin Investigation, 19 591, 1940

[49] DAVENPORT, H The ABC of Acid Base Chemistry, The Elements of

Physiological Blood—Gas Chemistry for Medical Students and Physicians, Third Edition Chicago, Chicago University Press, 1950

50 DAYMAN, H Mechanics of Airflow in Health and in Emphysema J Clin Investigation, 30 1175, 1951

51 DEXTER, L, DOW, J W, HAYNES, F W., WHITTENBERGER, J L, FERRIS, B G, GOODALE, W T AND HELLEMS, H. K Studies of the Pulmonary Circulation in Man at Rest Normal Variation and the Interrelations Between Increased Pulmonary Blood Flow, Elevated Pulmonary Arterial Pressure, and High Pulmonary "Capillary" Pressures J Clin Investigation, 29 602, 1950

52 DEXTER, L, WHITTNEBERGER, J L, GORLIN, R, LEWIS, B M, HAYNES, F W AND SPIEGEL, R J The Effect of Chronic Pulmonary Disease (Cor Pulmonale and Hypoxia) on the Dynamics of the Circulation in Man Tr A Physicians, 64 226, 1951

53 DEXTER, L, LEWIS, B M, HAYNES, F W, GORLIN, R AND HOUSSAY, E J Chronic Cor Pulmonale Without Hypoxia Bull New England M Cen, 14 69, 1952

54 DONALD, K W, RENZETTI, A, RILEY, R L, AND COURNAND, A Analysis of Factors Affecting Concentrations of Oxygen and Carbon Dioxide in Lung Gas and Blood J Applied Physiol, 4 497, 1952

55 DRESDALE, D T, SCHULTZ, M AND MICHTOM, R J Primary Pulmonary Hypertension I Clinical and Hemodynamic Study Am J Med, 11 686, 1951

56 DULFANO, M J AND SEGAL, M S Timed Vital Capacity in Bronchial Asthma J Allergy, In Press, 1953

57 DULFANO, M J AND SEGAL, M S The Use of Neo-Penil, a Diethylaminoethyl Ester of Penicillin, in Pulmonary Disease Dis of Chest, 23 136 1953

58 DULFANO, M J, MACK, F X AND SEGAL, M S N-Allyl Normorphine in the Treatment of Respiratory Acidosis In Press

59 ELLIS, L B AND BLOOMFIELD, R A Medical Progress, Cardiac Catheterization New England J Med, 243 339, 1950

60 ESCHER, D J W, WESTON, R E, LEINER, G, LEITER, L AND GOLDAT, S The Effect of Aminophyllin on Cardiac Output and Renal Hemodynamics in Man Fed Proc, 7 31, 1948

61 FERRER, M I, HARVEY, R M, CATHCART, R T, WEBSTER, C A, RICHARDS, D W, JR AND COURNAND, A Some Effects of Digoxin Upon the Heart and Circulation in Man, Digoxin in Chronic Cor Pulmonale Circulation, 1 161, 1950

62 FERRER, M I Personal Communication April, 1952

63 FLEISCHNER, F G Pathogenesis of Chronic Substantial (Hypertrophic) Emphysema Am Rev Tuberc, 62 45, 1950

64 FOWLER, W S Specific Tests of Pulmonary Function, in Methods in Medical Research, Vol 2 Edited by J H COMROE, JR Chicago, Year-book Publishers, Inc, 1950

BIBLIOGRAPHY

OWLER, N O, WESTCOTT, R N, HAUENSTEIN, V D, SCOTT, R C AND MCGUIRE, J Observations on Autonomic Participation in Pulmonary Arteriolar Resistance in Man J Clin Investigation, *29* 1387, 1950

GAENSLER, E A AND CARTER, M G Ventilation Measurements in Pulmonary Emphysema Treated with Pneumoperitoneum J Lab Clin Med, *35* 945, 1950

GAENSLER, E A Air Velocity Index, Numerical Expression of Functionally Effective Portion of Ventilation Amer Rev Tuberc *62* (*No 1A*) 17, 1950

GAENSLER, E A Analysis of the Ventilatory Defect by Timed Capacity Measurements Am Rev Tuberc, *64* 256, 1951

GAENSLER, E A Bronchospirometry I Review of the Literature J Lab Clin Med, *39* 917, 1952

GAENSLER, E A AND WATSON, T R, JR Bronchospirometry III Complications, Contraindications, Technique, and Interpretation J Lab Clin Med, *40* 223, 1952

GOLD, H, KWIT, N T, MODELL, W, HANLON, L W, KRAMER, M, GREENBERG, S, OTTO, H L, COTLOVE, E W, BENTON, J G, PERLMUTTER, M AND ZAHM, W A System for the Routine Treatment of the Failing Heart Am J Med, *3* 665, 1947

GORDON, B, MOTLEY, H L, THEODOS, P A, LANG, L P AND TOMASHEFSKI, J Considerations of the Clinical and Physiological Factors in the Treatment of Chronic Pulmonary Conditions Dis of Chest, *19* 271, 1951

GRAY, J S Pulmonary Ventilation and its Physiological Regulation Springfield, Charles C Thomas, 1950

GRAY, J S, BARNUM, D R, MATHESON, H W AND SPIES, S N Ventilatory Function Tests I Voluntary Ventilation Capacity J Clin Investigation, *29* 677, 1950

GREIFENSTEIN, F E, KING, R M, LATCH, S S AND COMROE J H, JR Pulmonary Function Studies in Healthy Men and Women 50 Years and Older J Applied Physiol *4* 641, 1952

GRISBY, M E, HAIGHT, T H AND FINLAND, M Some Clinical and Laboratory Observations on the Hydroiodide of Diethylaminoethyl Ester of Penicillin G (Neo-Penil) New England J Med, *247* 807, 1952

GROSS, D Investigations Concerning Vital Capacity Am Heart J, *25* 335, 1943

HALDANE, J S Respiration New Haven, Yale University Press, 1927

HAMMAN, L Spontaneous Mediastinal Emphysema Bull Johns Hopkins Hosp, *64* 1, 1939

HARKEN, D Personal Communication August, 1952

HARVEY, R M, FERRER, M I, RICHARDS, D W, JR AND COURNAND, A Influence of Chronic Pulmonary Disease on the Heart and Circulation Am J Med, *10* 719, 1951

HELLEMS, H K, HAYNES, F W AND DEXTER, L Pulmonary "Capillary" Pressure in Man J Applied Physiol, *2* 24, 1949

83 HERSCHFUS, J A, BRESNICK, E AND SEGAL, M. S Pulmonary Function Studies in Bronchial Asthma I In the Control State II After Treatment Am J Med, 14 23, 1953

84 HERXHEIMER, H G J Management of Bronchial Asthma London and Ontario, Butterworth & Co, 1952

85 HICKAM, J B AND CARGILL, W H [illegible] tion, 27 10, 1948

86 HURTADO, A, KALTREIDER, N L, FRAY, W. W, BROOKS, W D W, AND McCANN, W S Studies of Total Pulmonary Capacity and its Subdivisions VI Observations on Cases of Obstructive Pulmonary Emphysema J Clin Investigation, 13 1027, 1934

87 JOHNSON, J B, FERRER, M I, WEST, J R AND COURNAND, A The Relation Between Electrocardiographic Evidence of Right Ventricular Hypertrophy and Pulmonary Arterial Pressure in Patients with Chronic Pulmonary Disease Circulation, 1 536, 1950.

88 KALTREIDER, N L AND McCANN, W. S Respiratory Response During Exercise in Pulmonary Fibrosis and Emphysema J. Clin Investigation, 16 23, 1937

89 KETTY, S S, SHENKIN, H A AND SCHMIDT, C F. The Effects of Increased Intracranial Pressure on Cerebral Circulatory Functions in Man J Clin Investigation, 27 493, 1948

90 KETTY, S S, POLIS, B D, NADLER, C S AND SCHMIDT, C F. The Blood Flow and Oxygen Consumption of the Human Brain in Diabetic Acidosis and Coma J Clin Investigation, 27 500, 1948

91 KNIPPING, H W Dyspnoe Beitr Klin Tuberk 82·133, 1933

92 KORY, R C, ROEHM, D C, MENEELY, G R AND GOODWIN, R A, JR I Pulmonary Function and Circulatory Dynamics in Artificial Pneumoperitoneum Dis of Chest, In Press, 1953

93 KORY, R C, ROEHM, D C, MENEELY, G R AND GOODWIN, R. A, JR II Studies on Patients with Pneumoperitoneum as a Therapeutic Measure in Pulmonary Emphysema Dis of Chest, In Press, 1953

94 KOUNTZ, W B AND ALEXANDER, H. L Non-Obstructive Emphysema J A M A, 100 551, 1933

95 KOUNTZ W B AND ALEXANDER H L: Emphysema Medicine, 13 351, 1934

96 LAENNEC, R T G A Treatise on the Diseases of the Chest and Mediate Auscultation, Second Edition Translated from the French with Notes and a Sketch of the Author's Life by JOHN FORBES, London, T G Underwood, 1827

97 LEE, R C AND SILVERMAN, L An Apparatus for Measuring Airflow During Inspiration Rev Scient Instruments, 14 174, 1943

98 LENZI M Elimination of the Water-Soluble Contrast Medium in Bronchography "Functional Bronchography" Acta Radiol, 37 103, 1952

99 LIEBOW, A A, HALES, M R, HARRISON, W, BLOOMER, W AND LINDSAY,

G E Genesis and Functional Implications of Collateral Circulation of Lungs Yale J Biol and Med, 22 637, 1950

100 LILIENTHAL, J L, JR, RILEY, R L, PROEMMEL, D D AND FRANKE, R E An Experimental Analysis in Man of the Oxygen Pressure Gradient from Alveolar Air to Arterial Blood During Rest and Exercise at Sea Level and at Altitude Am J Physiol, 147, 199, 1946

101 LIPPELT, H Einfluss der Stenosenatmung auf Lungenventilation und Lungenvolumina beim Gesunden Beitr Klin Tuberk, 81 520, 1932

102 LIVINGSTONE, J L Physical Exercises for Asthma London, Research Council, Kings College, 1937

103 LUKAS, D S Pulmonary Function in a Group of Young Patients with Bronchial Asthma J Allergy, 22 411, 1951

104 MACKLIN, M T AND MACKLIN, C C Malignant Interstitial Emphysema of the Lungs and Mediastinum as an Important Occult Complication in Many Respiratory Diseases and Other Conditions An Interpretation of the Clinical Literature in the Light of Laboratory Experiment Medicine, 23 281, 1944

105 MALONEY, J V, JR, OTIS, A B, FENN, W O AND WHITTENBERGER, J L Effect of Positive Pressure Breathing on Air Flow Resistance of the Tracheobronchial Tree (abstract) J Clin Investigation, 29 832, 1950

106 MALONEY, J. V, JR Therapeutics of Pressure Breathing Bull New England M Center, 12 116, 1950

107 MALONEY, J V, JR AND WHITTENBERGER, J L Clinical Implications of Pressures used in the Body Respiratory Am J Med Sc, 221 425, 1951

108 MARKS, M O AND ZIMMERMAN, H A The Roentgen and Differential Diagnosis of Chronic Cor Pulmonale Am J Roentgenol 66 9, 1951

109 MATHESON, H W, SPIES, S N, GRAY, J S AND BARNUM, D R Ventilatory Function Tests II Factors Affecting the Voluntary Ventilation Capacity J Clin Investigation, 29 682, 1950

110 MAY, E Physical Therapy in Medical Diseases of the Chest Phy Therapy Rev, 32 121, 1952

111 MAYER, E AND RAPPAPORT, J Pulmonary Emphysema J of Mt Sinai Hosp, 12 505, 1945

112 McMICHAEL, J Pharmacology of the Failing Human Heart Springfield, Ill, Charles C Thomas, 1950

113 MENEELY G R AND KALTREIDER, N L The Volume of the Lung Determined by Helium Dilution Description of the Method and Comparison with Other Procedures J Clin Investigation, 28 129, 1949

114 MOTLEY, H L, COURNAND, A, WERKO, L, HIMMELSTEIN, A AND DRESDALE, D The Influence of Short Periods of Induced Acute Anoxia upon Pulmonary Artery Pressures in Man Am J Physiol, 150 315, 1947

115 MOTLEY, H L AND TOMASHEFSKI, J F Effect of High and Low Oxygen Levels and Intermittent Positive Pressure Breathing on Oxygen Transport in the Lungs in Pulmonary Fibrosis and Emphysema J Applied Physiol, 3 189, 1950

116 MOTLEY, H L Evaluation of Pulmonary Function Impairment by Phys

iologic Studies on 400 Unselected Cases of Hard and Soft Coal Miners with Respiratory Complaints Presented at the McIntyre Research Foundation Conference on Silicosis and Aluminum Therapy, Schumacher, Ontario, January 30, 1951.

117 Motley, H L and Tomashefski, J. F Treatment of Chronic Pulmonary Disease with Intermittent Positive Pressure Breathing I Evaluation by Objective Physiological Measurements A. M A Arch Ind Hyg, 6 1, 1952

118 Motley, H L Personal Communication

119 Pappenheimer, A M, Jr, Chairman Standardization of Definitions and Symbols in Respiratory Physiology Fed Proc, 9 602, 1950

120 Peters, G A, Prickman, L E, Koelsche, G A and Carryer, H M. Smoking and Asthma Proc Staff Meet, Mayo Clin, 27. 329, 1952

121 Piaggio-Blanco, R A, Piaggio-Blanco, R O and Caimi, R A Mejorías Sintomáticas del Enfisema por el Neumoperitoneo Arch Urug de Med, cir y especialid, 10 273, 1937

122 Prinzmetal, M and Kountz, W B Intrapleural Pressure in Health and Disease and its Influence on Body Function Medicine, 14 457, 1935

123 Proctor, D F and Hardy, J B Studies of Respiratory Air Flow. I Significance of the Normal Pneumotachogram Bull Johns Hopkins Hosp, 85 253, 1949

124 Proctor, D F, Hardy, J B and McLean, R Studies of Respiratory Air Flow II Observations on Patients with Pulmonary Disease Bull Johns Hopkins Hosp, 87 255, 1950

125 Rackemann, F M The Use of Drugs in Asthma J A M A, 114 1998, 1940

126 Rahn, H, Fenn, W O and Otis, A B Daily Variations of Vital Capacity, Residual Air and Expiratory Reserve Including a Study of the Residual Air Method J Applied Physiol, 1 725, 1949

127 Reich, L Der Einfluss des Pneumoperitoneums auf das Lungen Emphysema Wein Arch f inn Med, 8 245, 1924

128 Reichert, P and Roth, H The Ventilograph An Improved Recording Ventilometer and its Application J of Lab Clin Med, 25 1091, 1940

129 Riley, R L, Proemmel, D D and Franke, R E A Direct Method for Determination of Oxygen and Carbon Dioxide Tensions in Blood J Biol Chem, 161 621, 1945

130 Riley, R L, Himmelstein, A, Motley, H L, Weiner, H M and Cournand, A Studies of Pulmonary Circulation at Rest and During Exercise in Normal Individuals and in Patients with Chronic Pulmonary Disease Am J Physiol, 152 372, 1948

131 Riley, R L and Cournand, A Analysis of Factors Affecting Partial Pressures of Oxygen and Carbon Dioxide in Gas and Blood of Lungs Theory J Applied Physiol, 4 77, 1951

132 Roughton, F J W and Scholander, P F Micro Gasometric Estimation of the Blood Gases I Oxygen J Biol Chem 148 541, 1943

133 SARNOFF, S. J., HARDENBERG, E. AND WHITTENBERGER, J. L. Electrophrenic Respiration. Science, *108*: 482, 1948.

134 SCHOLANDER, P. F. AND ROUGHTON, F. J. W. Micro Gasometric Estimation of the Blood Gases. IV. Carbon Dioxide. J. Biol. Chem., *148*: 573, 1943.

135 SCHOLANDER, P. F. AND EVANS, H. J. Microanalysis of Fractions of a Cubic Millimeter of Gas. J. Biol. Chem., *169*: 551, 1947.

136 SCOTT, R. W. AND GARVIN, C. F. Cor Pulmonale: Observations in Fifty Autopsy Cases. Am. Heart J., *22*: 56, 1941.

137 SEGAL, M. S. AND RYDER, C. M. Penicillin Inhalation Therapy. New England J. Med., *236*: 132, 1947.

138 SEGAL, M. S. AND HERSCHFUS, J. A. ACTH and Cortisone in the Management of the Hypersensitivities with Particular Reference to Bronchial Asthma. Ann. Allergy, *8*: 786, 1950.

139 SEGAL, M. S. The Management of the Patient with Severe Bronchial Asthma. Springfield, Ill., Charles C Thomas, 1950.

140 SEGAL, M. S. AND HERSCHFUS, J. A. ACTH and Chronic Bronchial Asthma. G. P., *3*: 39, 1951.

141 SEGAL, M. S., HERSCHFUS, J. A. AND BRESNICK, E. Bronchial Asthma—A Review of the Literature. Ann. Allergy, *9*: 782, 1951.

142 SEGAL, M. S. AND HERSCHFUS, J. A. Oxygen Therapy: Description of a New Face Tent. Bull. New England M. Center, *13*: 244, 1951.

143 SEGAL, M. S. AND HERSCHFUS, J. A. Intravenous ACTH Therapy in the Treatment of Bronchial Asthma. Dis. of Chest, *20*: 575, 1951.

144 SEGAL, M. S. AND HERSCHFUS, J. A. Pituitary Adrenocorticotropic Hormone (ACTH) in the Management of Severe Chronic Bronchial Asthma, in Proceedings of the Second Clinical ACTH Conference. Edited by J. R. MOTE, Philadelphia, The Blakiston Co., 1951.

145 SEGAL, M. S., HERSCHFUS, J. A. AND DULFANO, M. J. A Simple Method for the Determination of Vital Capacity—Time Relationships. Dis. of Chest, *22*: 123, 1952.

146 SEGAL, M. S., DULFANO, M. J. AND HERSCHFUS, J. A. Recent Advances in the Physiology and Treatment of Bronchial Asthma. Quart. Rev. Allergy, *6*: 399, 1953.

147 SILVERMAN, L., LEE, R. C. AND DRINKER, C. K. A New Method for Studying Breathing, With Observations Upon Normal and Abnormal Subjects. J. Clin. Investigation, *23*: 907, 1944.

148 SILVERMAN, L. Respiratory Air Flow Characteristics and Their Relation to Certain Lung Conditions Occurring in Industry. J. Indust. Hyg. and Toxicolog., *28*: 183, 1946.

149 SINGER, R. B. AND HASTINGS, A. B. An Improved Clinical Method for the Estimation of Disturbances of the Acid-Base Balance of Human Blood. Medicine, *27*: 223, 1948.

149a SINGER, R. AND HASTINGS, A. B. *Quoted by* COMROE, J. H., JR. Interpretation of Commonly Used Pulmonary Function Tests. Am. J. Med., *10*: 356, 1951.

151 Smart, R H, Davenport, C K. and Pearson, G W Intermittent Positive Pressure Breathing in Emphysema of Chronic Lung Diseases J A M A, *150* 1385, 1952.

152 Sokolow, M and Lyon, T P. The Ventricular Complex in Right Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads Presented Before the American Fed of Clin Res., Chicago, April, 1947

153 Spain, D M and Handler, B J Chronic Cor Pulmonale. Sixty Cases Studies at Necropsy Arch. Int Med, *77* 37, 1946

154 Starr, I, Gamble, C J, Margolies, A, Donald, J S, Jr, Joseph, N, and Eagle, E A Clinical Study of the Action of 10 Commonly Used Drugs on Cardiac Output, Work, and Size, On Respiration, on Metabolic Rate and on the Electrocardiogram J Clin Investigation, *16* 799, 1937

155 Stieglitz, E J The Histologic Detection of Iodides J Pharmacol & Exper Therap, *22* 89, 1924

156 Sussman, M L, Steinberg, M F and Grishman, A · Contrast Visualization of the Heart and Great Vessels in Emphysema Am J. Roentgenol, *47* 368, 1942

157 Trimble, H G Personal Communication, 1952

158 Truitt, E B, Jr, McKusick, V A and Krantz, J C, Jr Theophylline Blood Levels After Oral, Rectal and Intravenous Administration, and Correlation with Diuretic Action J Pharmacol & Exper Therap, *100* 309, 1950

159 Tuft, L and Levin, N M Studies of the Expectorant Action of Iodides Am J M Sc, *203* 717, 1942

160 Turner, H, James, D F and Merrill, A. J Studies on the Mechanism of Reduction in Renal Flow in Heart Failure Preliminary Report Am J Med, *6* 619, 1948

161 Ungar, L and Wolf, A A Treatment of Bronchial Asthma, A Survey of the Value of Treatment in 459 Cases During Twenty Years J A M A, *121* 325, 1943

162 Van Liere, E J Anoxia—Its Effect on the Body Chicago, Chicago University Press, 1942

163 Van Slyke, D D and Neill, J M Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement J Biol Chem *61* 523, 1924

164 Vaquez, H and Lutembacher, R La Question de L'Ouabaine Arnaud Presse Med, *36* 129, 1928

165 Vogl, A and Esserman, P Aminophyllin as a Supplement to Mercurial Diuretics in Intractable Congestive Heart Failure J A M A, *147* 625, 1951

166 Waxler, S and Schack, I · Administration of Aminophyllin J A M A, *143* 736, 1950

167 Weinstein, L The Spontaneous Occurrence of New Bacterial Infections During the Course of Treatment with Streptomycin or Penicillin Am J M Sc, *214* 56, 1947

168 WEST, H F Clinical Studies on Respiration VI Comparison of Various Standards for Normal Vital Capacity of the Lungs Arch Int Med, *26* 306, 1920

169 WEST, J R, BALDWIN, E DEF, COURNAND, A AND RICHARDS, D W, JR Physiopathologic Aspects of Chronic Pulmonary Emphysema Am J Med, *10* 481, 1951

170 WESTCOTT, R N, FOWLER, N O, SCOTT, R C, HAUENSTEIN, V D AND MCGUIRE, J Anoxia and Human Pulmonary Vascular Resistance J. Clin Investigation, *30* 957, 1951

171 WESTERMARK, N Roentgen Studies of the Lungs and Heart Minneapolis, University of Minnesota Press, 1948

172 WHITTENBERGER, J L AND SARNOFF, S J Physiologic Principles in the Treatment of Respiratory Failure M Clin North America, *34* 1335, 1950

173 WHITTENBERGER, J L Lung Volume and Air Flow Characteristics in Asthma, in Treatment of Asthma, Edited by H A ABRAMSON Baltimore, Williams & Wilkins, 1951

174 WOLFE, W A AND CARLSON, L D Studies of Pulmonary Capacity and Mixing with the Nitrogen Meter J Clin Investigation, *29* 1568, 1950

175 WRIGHT, G W, PLACE, R AND PRINCI, F The Physiological Effects of Pneumoperitoneum upon the Respiratory Apparatus Am Rev Tuberc, *60* 706, 1949

176 ZIMMERMAN, H A Study of the Pulmonary Circulation Dis of Chest, *20* 46, 1951

151 SMART, R. H., DAVENPORT, C. K. AND PEARSON, G. W.: Intermittent Positive Pressure Breathing in Emphysema of Chronic Lung Diseases. J. A. M. A., 150: 1385, 1952.
152 SOKOLOW, M. AND LYON, T. P.: The Ventricular Complex in Right Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads. Presented Before the American Fed. of Clin. Res., Chicago, April, 1947.
153 SPAIN, D. M. AND HANDLER, B. J.: Chronic Cor Pulmonale. Sixty Cases Studies at Necropsy. Arch. Int. Med., 77: 37, 1946.
154 STARR, I., GAMBLE, C. J., MARGOLIES, A., DONAL D, J. S., JR., JOSEPH, N. AND EAGLE, E.: A Clinical Study of the Action of 10 Commonly Used Drugs on Cardiac Output, Work, and Size; On Respiration, on Metabolic Rate and on the Electrocardiogram. J. Clin. Investigation, 16: 799, 1937.
155 STIEGLITZ, E. J.: The Histologic Detection of Iodides. J. Pharmacol. & Exper. Therap., 22: 89, 1924.
156 SUSSMAN, M. L., STEINBERG, M. F. AND GRISHMAN, A.: Contrast Visualization of the Heart and Great Vessels in Emphysema. Am. J. Roentgenol., 47: 368, 1942.
157 TRIMBLE, H. G.: Personal Communication, 1952.
158 TRUITT, E. B., JR., MCKUSICK, V. A. AND KRANTZ, J. C., JR.: Theophylline Blood Levels After Oral, Rectal and Intravenous Administration, and Correlation with Diuretic Action. J. Pharmacol. & Exper. Therap., 100: 309, 1950.
159 TUFT, L. AND LEVIN, N. M.: Studies of the Expectorant Action of Iodides. Am. J. M. Sc., 203: 717, 1942.
160 TURNER, H., JAMES, D. F. AND MERRILL, A. J.: Studies on the Mechanism of Reduction in Renal Flow in Heart Failure. Preliminary Report. Am. J. Med., 5: 619, 1948.
161 UNGER, L. AND WOLF, A. A.: Treatment of Bronchial Asthma, A Survey of the Value of Treatment in 450 Cases During Twenty Years. J. A. M. A., 121: 325, 1943.
162 VAN LIERE, E. J.: Anoxia—Its Effect on the Body. Chicago, Chicago University Press, 1942.
163 VAN SLYKE, D. D. AND NEILL, J. M.: Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement. J. Biol. Chem., 61: 523, 1924.
164 VAQUEZ, H. AND LUTEMBACHER, R.: La Question de L'Ouabaine Arnaud. Presse Med., 36: 129, 1928.
165 VOGL, A. AND ESSERMAN, P.: Aminophyllin as a Supplement to Mercurial Diuretics in Intractable Congestive Heart Failure. J. A. M. A., 147: 625, 1951.
166 WAXLER, S. AND SCHACK, I.: Administration of Aminophyllin. J. A. M. A., 143: 736, 1950.
167 WEINSTEIN, L.: The Spontaneous Occurrence of New Bacterial Infections During the Course of Treatment with Streptomycin or Penicillin. Am. J. M. Sc., 214: 56, 1947.

68 West, H F Clinical Studies on Respiration VI Comparison of Various Standards for Normal Vital Capacity of the Lungs Arch Int Med, *25* 306, 1920

69 West, J R, Baldwin, E deF, Cournand, A and Richards, D W, Jr Physiopathologic Aspects of Chronic Pulmonary Emphysema, Am J Med, *10* 481, 1951

70 Westcott, R N, Fowler, N O, Scott, R C, Hauenstein, V D and McGuire, J, Anoxia and Human Pulmonary Vascular Resistance J Clin Investigation, *30* 957, 1951

71 Westermark, N Roentgen Studies of the Lungs and Heart Minneapolis, University of Minnesota Press, 1948

72 Whittenberger, J L and Sarnoff, S J Physiologic Principles in the Treatment of Respiratory Failure M Clin North America, *34* 1335, *1950*

73 Whittenberger, J L Lung Volume and Air Flow Characteristics in Asthma, in Treatment of Asthma, Edited by H A Abramson Baltimore, Williams & Wilkins, 1951

74 Wolfe, W A and Carlson, L D Studies of Pulmonary Capacity and Mixing with the Nitrogen Meter J Clin Investigation, *29* 1568, 1950

75 Wright, G W, Place, R and Princi, F The Physiological Effects of Pneumoperitoneum upon the Respiratory Apparatus Am Rev Tuberc, *60* 706, 1949

76 Zimmerman, H A Study of the Pulmonary Circulation Dis of Chest, *20* 46, 1951

Index